Volume XXI Number 7

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

JULY
1960

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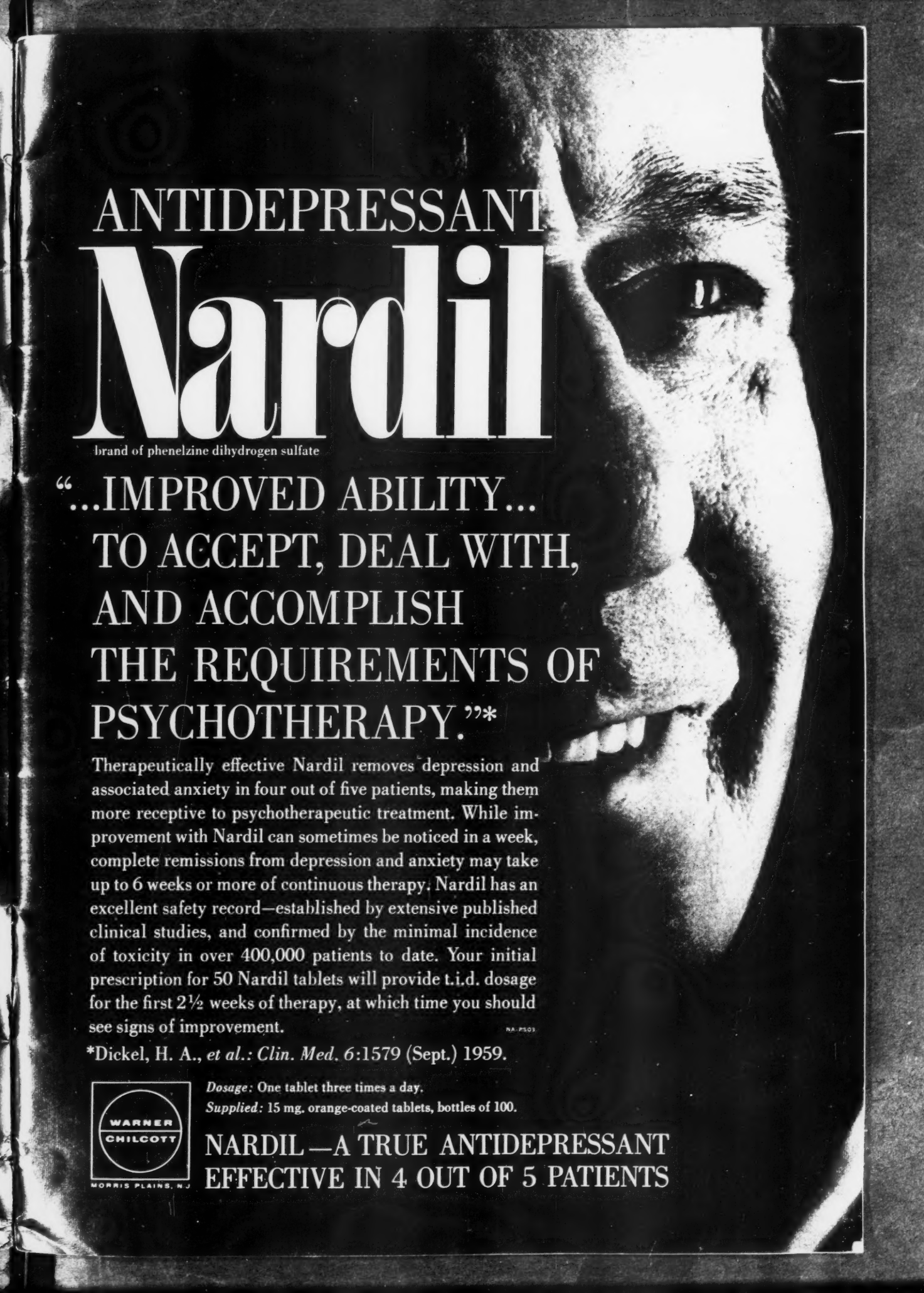

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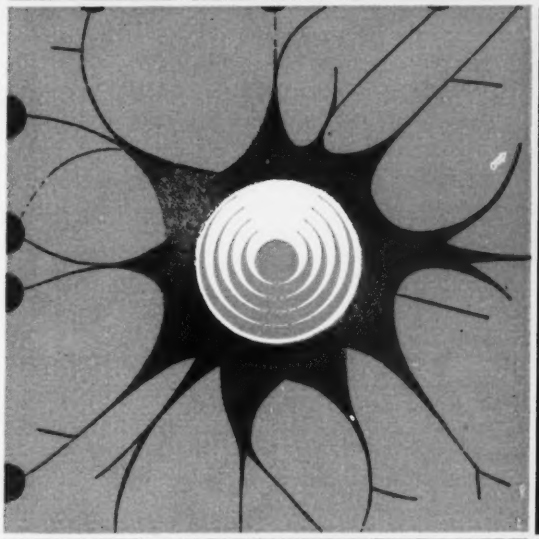

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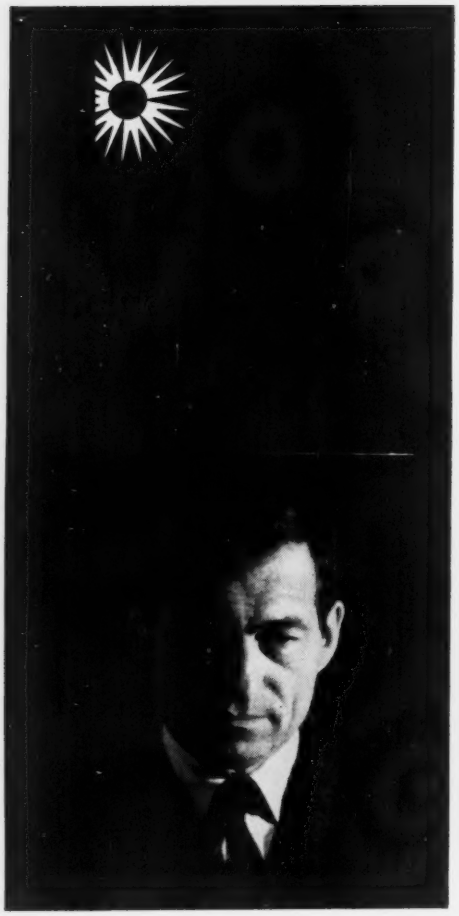

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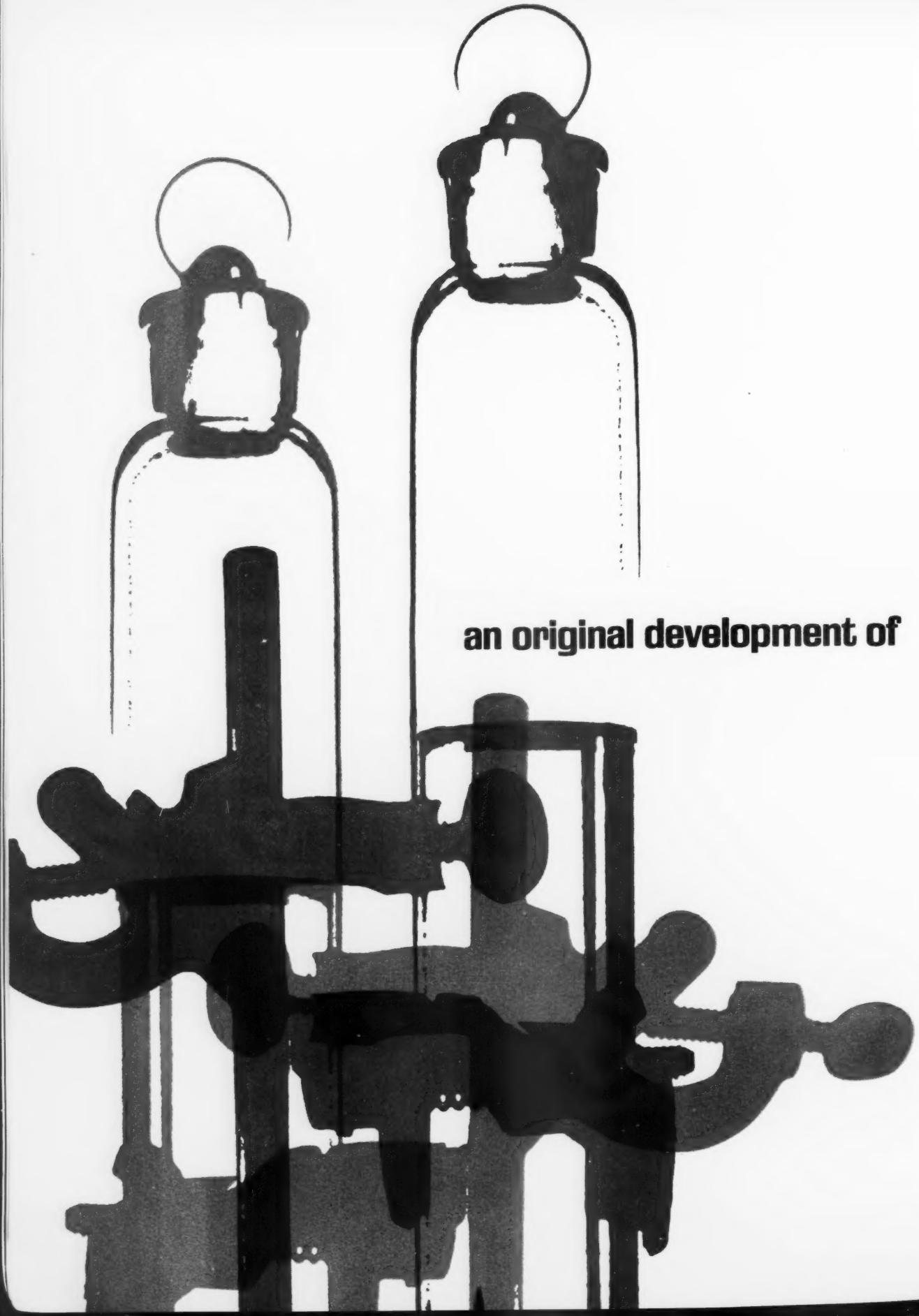

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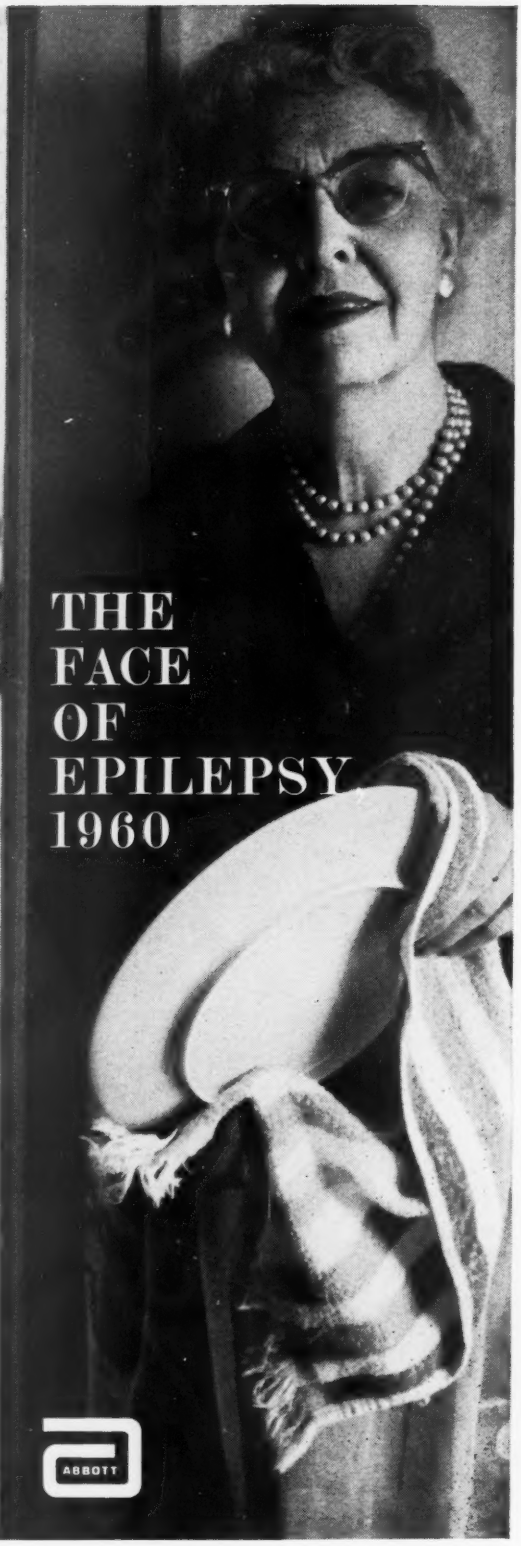

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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Evaluation of Change in Drug-Treated Psychiatric Patients

ARNOLD J. FRIEDHOFF, M.D., GILDA ROSENBLATT, M.S., FRANCES A. LYNN, M.N., MURRAY ALPERT, M.S., and S. BERNARD WORTIS, M.D.

An evaluation of change in drug-treated psychiatric patients is frequently based upon observations or tests carried out in a standard fashion. An adequate measure of change in status should reflect many factors related to change and should be reasonably reproducible by different observers. If, in addition, the information can be assembled in a quantitative fashion, results can be more readily compared and evaluated.[1]

No single measuring instrument meets all those requirements. In general, the more sensitive approaches are less readily reproducible and less quantitative. In order to combine the features of reproducibly and sensitivity, investigators have used different methods of evaluation simultaneously.[2]

This study was undertaken as part of a program to develop a multifactorial method for the evaluation of change in drug-treated psychiatric patients. The following five areas of psychological function were studied:

General Clinical Status

In this report general clinical status refers to the usual procedure for evaluating psychiatric patients by means of a history and an examination of physical and mental status. Observations involved in this approach are usually made during interviews with the patient, and also frequently contain information derived from observations of the patient's function in a ward setting. The clinical examiner incorporates a great deal of impressionistic data, some of which may not lend itself to clear definition. As a result, it is often difficult to assess the exact areas considered by the examiner in making his overall clinical evaluation.

At the conclusion of a study the general clinical status is usually recorded as either *improved* or *unimproved.* In addition, the degree of improvement is frequently modified by such terms as *slightly* or *moderately.* Although the clinical examination may be highly sensitive to many subtle factors indicating change, it is nevertheless only grossly quantifiable. In the present study patients were evaluated clinically by means of a psychiatric examination as described.

Alterations in Symptoms

This area of evaluation refers to an appraisal of changes in psychiatric symptoms by means of a standardized rating scale. Symptoms such as hallucinations, delusions, psychomotor retardation and other similar disturbances are evaluated and scored on the rating scale by a clinician or other observer at the termination of a clinical examination.

Data in this form is more readily quantifiable than from the clinical examination. On the other hand, it is less sensitive to subtle changes occurring from one interview to the next and reflects little of the effects of the illness on performance not specifically delineated in the rating scale. In this study the Lorr Multidimensional Scale for Rating Psychiatric Patients[3] was used.

From Psychopharmacology Research Unit, Department of Psychiatry and Neurology, New York University Bellevue Medical Center.

This study is part of a project supported by a research grant (No. MY-2716) from the National Institutes of Health, U.S. Public Health Service.

Performance on a Standard Task

It has been well established that psychiatric illness can affect many areas of function not specifically related to the symptomatology of the disorder.[4] These areas of function, however, are not ordinarily rated in standard evaluation procedures such as those mentioned above.

Performance data can usually be obtained in highly quantitative form. A further advantage is that this data reflects areas of psychological function not usually incorporated in the clinical evaluation or in the symptom rating scale. One such task which reflects the effects of psychiatric disturbance is the intelligence test.

A pilot study done with a group of patients prior to the present study indicated that the Wechsler - Bellevue Intelligence Scale, Form I,[4] was a suitable instrument for measuring changes in drug-treated patients. It was found that these changes were reflected primarily in the four subtests, *Comprehension, Similarities, Picture Completion* and *Digit Symbol.* These subtests were administered in the present study.

Approach to a Task

As used in this study, this area of evaluation refers to the mental set with which the patient approaches a task. This was evaluated in order to determine the relationship of change in mental set to change in performance. It was felt that improvement in performance would in part be a result of change in mental set. A Task Behavior Scale (TBS) devised by one of us (G.R.) was employed to measure the patient's approach to the Wechsler-Bellevue Intelligence Scale.

TASK BEHAVIOR SCALE

1. COOPERATION:
   - 0—Good: No urging needed
   - 1—Fair: Little urging
   - 2—Poor: Much urging
   - 3—Very Poor: Refuses completely
2. GRASP OF INSTRUCTIONS
   - 0—Good: Understands quickly
   - 1—Fair: Occasional repetition and correction required
   - 2—Poor: Constant repetition and correction required
   - 3—Very Poor: Unable to understand
3. MANNER DURING TEST
   - 0—Good: Relaxed and interested
   - 1—Fair: Uneasy (or) shows some annoyance
   - 2—Poor: Distressed (or) competitive and tense
   - 3—Very Poor: Distressed and withdrawn (or) hostile and abusive
4. ATTENTION TO TASK
   - 0—Good: Complete attention
   - 1—Fair: Usually attentive
   - 2—Poor: Attention limited and wandering
   - 3—Very Poor: Complete inattention
5. ABILITY TO EVALUATE OWN PERFORMANCE
   - 0—Good: Consistent with objective performance
   - 1—Fair: Somewhat inconsistent with objective performance
   - 2—Poor: Grossly inconsistent with objective performance
   - 3—Very Poor: No recognition of quality
6. RAPPORT
   - 0—Good: Friendly, easy accord
   - 1—Fair: Reserved
   - 2—Poor: Strained, infrequent accord
   - 3—Very Poor: No inter-personal contact

Spontaneous Performance Of Everyday Behavior

Patients can sometimes mobilize themselves for a testing session, but often cannot sustain the level of performance achieved during the testing period. It is necessary, therefore, to develop methods for evaluating spontaneous behavior which will reflect the patient's usual performance. This area is being studied at the present time and will not be discussed in the present report. In this study, therefore, several approaches have been used to measure changes both in the symptoms of psychiatric syndromes and in some related types of performance.

Procedure

Selection of Subjects

Subjects were selected for this study by screening all new admissions to the disturbed and semi-disturbed adult wards of Bellevue Hospital, Psychiatric Division. Subjects were included in the study according to the following criteria:

1. Unequivocal diagnosis of schizophrenia made independently by two psychiatrists.
2. Between 18 and 60 years of age.
3. No history of excessive use of alcohol.
4. No use of drugs up to two weeks prior to admission.

5. No evidence of illness other than schizophrenia.
6. Ability to cooperate in all test procedures.

Thirty patients were selected, 7 males and 23 females, between the ages of 19 and 54 (mean age: 33.8 years). See Table I for a more detailed classification.

Method of Treatment

All patients selected were placed on placebo for a period of three to seven days to establish a base line of vital signs and somatic complaints. One-third of the patients were then treated with SKF #5354, one-third with SKF #6023, and one-third with placebo. Both active drugs are phenothiazine derivatives with effects similar to those of chlorpromazine. The daily dose range for patients receiving SKF #5354 was between 75 mg. and 225 mg. and for patients on SKF #6023, between 3 mg. and 25 mg.

In a simultaneous but independent study, SKF #5354 was found to be a highly effective drug in the treatment of schizophrenia, SKF #6023 was less effective, and placebo least effective. The two drugs and the placebo provided a useful range of response from *marked improvement* to *no change.* Therefore, for the present study, results from all three treatments were pooled prior to analysis.

Further details on the administration of these drugs will not be presented here since this paper is a report on methods of evaluation of change in drug-treated patients and not a study of the particular drugs used.

Method of Evaluation

The clinical status of each patient was evaluated by a psychiatrist before and during treatment. The following categories were used to designate changes in clinical status:

Improved: Changes in condition ranging from complete or nearly complete remission of all symptoms to partial remission of symptoms which appreciably altered the status of the patient or lessened the care necessary.

Unimproved: (1) no perceptible change in the patient's condition; (2) slight improvement which did not alter the status of the patient, nor lessen his care; (3) exacerbation of illness and increased difficulties in management.

The patients were evaluated by a second psychiatrist and a nurse, using the Lorr Scale. The psychiatrist completed the first section of the scale and, independently of his ratings, the nurse completed the ward observation section. These ratings were made independent of the first psychiatrist's clinical impressions.

The four subtests of the Wechsler-Bellevue Intelligence Scale—*Comprehension, Similarities, Picture Completion* and *Digit Symbol*—were administered to each patient by a psychologist before and after treatment. The psychologist also evaluated each patient's approach to these tests by means of the TBS. The double-blind method was used throughout.

Results

Based on the clinical evaluation, the patients were divided into two groups—*improved* and *unimproved.* As a result of all three treatments, SKF #5354, SKF #6023, and placebo, 16 patients improved and 14 patients were unimproved. Average age, sex, diagnosis, and mean duration of treatment

TABLE I

Classification of Patients

	Improved		Unimproved	
Number of Patients	16		14	
Sex	4 Male	12 Female	3 Male	11 Female
Mean Age	33.9	(Range 19-54)	33.5	(Range 21-52)
DIAGNOSIS				
Paranoid	4 Acute	5 Chronic	2 Acute	9 Chronic
Undifferentiated	2 "	2 "	—	3 "
Catatonic	1 "	—	—	—
Schizo-Affective	—	2 "	—	—
Duration of Treatment (Mean Days)	21.3	(Range 14-31)	21.9	(Range 11-61)

were similar for both the improved and unimproved groups. Table I is a classification of the patients in each group according to the usual criteria.

A summary of the results on each of the tests that were used for evaluation will be found in Table II. It will be noted that initially there were no significant differences on any of the tests between those subjects who ultimately improved clinically and those who remained unimproved clinically. At the end of treatment, however, a significant difference was found between the change scores of the improved patients as compared with those of the unimproved patients on the Lorr Scale, the TBS, the total score of the four Wechsler-Bellevue subtests, and three of the subtests themselves. The change scores on the Similarities test for the improved group was not significantly different from those of the unimproved group. This subtest, therefore,, did not significantly reflect a change coinciding with improvement as measured clinically.

We were interested in determining whether any of the tests reflected decrements which might be attributable to drug toxicity. In order to evaluate this possibility, the unimproved patients were divided into two groups according to whether they received active drug or placebo. These groups were then compared on the basis of results obtained on each test. Our reasoning was that if toxic effects were reflected in any of the tests, the scores of the unimproved drug-treated patients should increase less or decrease more after treatment than those of the unimproved placebo patients.

Table III demonstrates that there is little to support this hypothesis. Statistical analysis of the data shows that none of the scores of the unimproved drug group are significantly different from those of the unimproved placebo group. A similar comparison with improved patients was not possible since only one patient showed any appreciable improvement on placebo.

Discussion

Results found in this study demonstrate that the Lorr Scale, the TBS, and three of the four subtests of the Wechsler-Bellevue Scale can significantly discriminate between improved and unimproved patients evaluated from the clinical viewpoint.

Although there may be some overlap, each of these tests evaluates a somewhat different aspect of the patient's performance. It is felt, therefore, that an appraisal of the patient from each of these standpoints will provide a more balanced approach to the evaluation of drug treatment than is possible with any single test. Results from the TBS, which reflects the patient's approach to a standard task, suggest that a great deal of the improved performance on the Wechsler-Bellevue subtests is the result of an improved approach to the tests.

It has been previously established that psychiatric disturbances affect intelligence test performance.[4] In the present study it was demonstrated that improvement in psy-

TABLE II

Summary of Test Results on Improved and Unimproved Patients Treated with SKF #5354, SKF #6023 or Placebo

	INITIAL SCORES					CHANGE SCORES				
	Improved N: 16		Unimproved N: 14			Improved N: 16		Unimproved N: 14		
	Mean	S.D.	Mean	S.D.	P*	Mean	S.D.	Mean	S.D.	P
Lorr Scale	47.6	13.9	42.7	10.1	NS	25.9	19.1	3.9	9.2	.001
Wechsler-Bellevue										
Comprehension	5.4	2.6	6.5	2.8	NS	3.8	2.4	1.8	2.8	.05
Similarities	8.3	3.5	8.1	3.3	NS	2.0	2.7	0.7	2.5	NS
Picture Completion	6.0	4.6	7.1	3.6	NS	3.0	1.7	1.2	2.5	.05
Digit Symbol	4.6	3.6	7.3	4.9	NS	3.8	3.3	0.6	2.7	.01
Total	24.3	11.5	29.0	13.2	NS	12.6	6.0	4.3	8.6	.01
TBS	8.5	4.1	6.0	4.2	NS	5.1	3.5	1.8	2.9	.01

*Probabilities of .05 or greater are reported. All others are shown as NS (not significant).

chiatric status results in improved performance on three subtests of the Wechsler-Bellevue. This does not signify that patients have increased intelligence as a result of treatment. Rather, as shown by the results of the TBS, their ability to cooperate with the examiner and to apply themselves has been heightened by an improvement in psychiatric status.

A Comparison of Unimproved Drug and Placebo Treated Patients

	Drug Group Mean Values No: 5		Placebo Group Mean Values N: 9	
	Initial Score	Change Score	Initial Score	Change Score
Lorr Scale	41.8	1.8	43.2	5.0
Wechsler-Bellevue				
Comprehension	6.4	2.0	6.6	1.7
Similarities	8.2	0.6	8.1	0.8
Picture Completion	6.2	2.2	7.7	0.7
Digit Symbol	7.4	1.8	7.2	—0.1
Total	28.2	6.6	29.6	3.1
TBS	6.0	2.4	6.0	1.3

Some investigators have reported only slight increments[5] or decrements[6] in performance as a result of tranquilizing drug treatment. However, this disparity in results probably reflects a difference in the type of subject chosen and the kind of drug used by each investigator. It should be noted that our subjects were good candidates for drug treatment and over 50 per cent of the entire group improved considerably as a result of this therapy.

The data from the present study suggests a useful, simple and successful method for the evaluation of psychotropic drugs. It involves (1) random assignment of patients to either a drug or placebo group, (2) use of double-blind methodology, and (3) evaluation of patients by means of clinical impression, the Lorr Scale, three subtests of the Wechsler-Bellevue Scale, and the TBS. Each instrument should be administered by a different person and the results should be obtained without knowledge of the results found by other investigators. In our study, results from these various approaches confirmed one another. The quantitative and semi-quantitative nature of the tests used in this study also make it possible to compare results from independent studies.

Summary

1. Thirty schizophrenic patients were treated with either one of two experimental drugs or with placebo.

2. Prior to initiation of treatment and at termination of treatment, each patient was evaluated clinically and by means of the Lorr Multidimensional Scale, four subtests of the Wechsler-Bellevue Intelligence Scale, and a Task Behavior Scale.

3. All the tests used, except the similarities test of the Wechsler-Bellevue Scale, significantly reflected a change in status when compared with the clinical evaluation.

4. This multifactorial method of evaluation provides a sensitive, quantitative procedure for evaluating changes in drug-treated psychiatric patients.

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Practice of Psychiatry in a Medium Size Community

PETE C. PALASOTA, M.D.

Many questions arise when we hear of one of our colleagues going into a small community to practice psychiatry. Right away, we want to know why he is going to such a small place. We also want to know if it is large enough to support a psychiatrist. Does he have proper facilities for the care of patients. Will he be accepted in the community? What sort of person is he? What kind of training does one need prior to embarking on such a venture? I would like to describe my experiences in two communities, one with a population of about 45,000 and the other having a population of some 70,000. There have been many similarities in these two practices that have been strikingly noticeable, at times amusing and certainly worth an attempt to chronicle. The subject matter of this presentation may be neither new, revolutionary, or earth shaking, but, perhaps, will be stimulating.

First of all, it is not new because the practice of psychiatry remains essentially the same in a small community as in a larger one. As for the techniques that are employed, they are identical. It is not new because inroads have been well paved by many of our colleagues who pioneered the practice of psychiatry in the small communities. Men such as Blocker Joslyn in Atlanta, Texas, Pat Hogan in Bristol, Tennessee, Tom Hall in Macon, Georgia, Ed Grice in Odessa, Texas, and George Constant in Victoria, Texas, are only a few of the many psychiatrists with interest and daring enough to leave the large city with its gleaming citadels of medicine to carry the cause of psychiatry to the hinterlands—to the small community.

The practice of psychiatry in a small community is not revolutionary because, as I have said, no new techniques have been developed in many years. However, with an apparent increase in the number of behavioral and adjustment problems that have developed within our complex culture as compared to the former large percentage of neuroses and psychoses our present long accepted therapeutic techniques may need revision. I am sure that many of you find that some of the techniques developed in the Victorian era simply do not adequately solve the problem as it has evolved today. Strict Freudian analysis cannot meet all the demands of mental illness and never was intended to do so. Perhaps in time part of this problem will be solved by this pioneer—this "general psychiatrist" as it were. It is entirely possible that as a result of this returning to small communities and helping to meet the problem where it begins as well as the possibility that our culture will outgrow some of our previous concepts that a new approach to many of these problems will develop.

Lastly, this subject matter is not earth shaking because it is a natural development brought on by the necessities of this culture which is so complex and rapidly changing. The changes are inevitable because we, as psychiatrists, have not found the answer to satisfy the magnitude of the problem of mental health, and we are still groping for answers. Only with daring enough to try something new may we find answers.

What do you suppose happens when a new psychiatrist moves to town, the first one in a small community? Interesting things, I assure you and with amusing analytical overtones. I noticed in both communities a sort of initial rallying around the new psychiatrist of what I call "do gooders"—people trying either to impress the psychiatrist or with some particular ax to grind. It has been interesting also that many of these people wind up coming to the office as patients later. This group is usually followed by an inquisitive group of people who want to see what a flesh and blood psychiatrist really looks like. Some of them are disappointed because he is not at all like the one on tele-

Read at the Annual Meeting of the Southern Psychiatric Ass'n, Oct. 1959.

vision or in the movies, and a few are glad that he is not, although most of them, without realizing it, project the same magical powers to him as to the actor on TV. I have had more than one patient enter my office and seriously ask me, "Where is your couch?" I have had many patients come into the office and ask for "some of that truth serum so I can see what is wrong." With the steady bombardment that the public is getting about hypnosis, there is hardly a day goes by but that someone doesn't come in wanting to be hypnotized and have all their difficulties magically removed.

By the time the inquisitive have come and gone, the people who are interested in psychiatry because it is a "fad" begin making their presence known. These, of course, are not too difficult to spot, and, following closely behind, are the people really in need of psychiatric help. This occurs when they begin to hear some good things about the new psychiatrist, when they begin having less of the feeling of the stigmata which are usually attached to mental illness. This can be very marked in a small community. These groups overlap and, though they are not hard to separate, it generally takes a couple of years to know the community and, incidentally, for the community to know the psychiatrist and be able to depend on him.

Also in this interval, the many facets of a small community such as the social, economic, and cultural strata can be more easily distinguished than they can in a large community. Local community pride and esprit de corps sometimes become closely intermingled within the social and cultural parts of this community. I am sure that men in larger cities are aware of these things, but on the miniature scale of a small community one can see the machinery in operation and the people who run the machinery.

The problem of referrals in a small community is important, and it behooves the new psychiatrist to have a broad background in what I call "general psychiatry." He must be ingenious and, at times, diplomatic. After all, the referring physician wants help for his patient, not a beautifully written analytical report ending with the statement that the prognosis is poor, and, therefore, the patient cannot be helped. I remember one case that was sent because of intractable abdominal pain. The simple process of doing a pelvic exam revealed a mass in the cul de sac. The problem of how to be diplomatic with the referring physician was an immediate one and, I am happy to say, worked out smoothly in this case. Part of the job of the psychiatrist is in educating the referring physician or physicians in his area as to what can and what cannot be treated. This, in the long run, is a great help to the psychiatrist as well as helping the patient and the referring physician. Surprisingly enough, many referring physicians will not send patients to any specialist who does not refer the patient back home when the treatment is finished and, consequently, may refer patients as far away as he possibly can so that they will be sure to come back home. Helping the referring physician to understand realistic goals in treatment rather than having either the patient or the doctor think in terms of some magical power which will cure the patient again helps all concerned. This willingness to be realistic and help the patient and referring physician be realistic is not to be confused with willingness to try to help anywhere needed be the prognosis good or bad. The referring physician many times will tell the patient, "This psychiatrist that I am going to send you to can get you well very easily." Or, he may say something like, "I am going to send you to a specialist." Many times I have had the feeling that anybody fifty miles away from home, practicing medicine is a specialist, and patients come with exactly that attitude.

The psychiatrist in a small community, in addition to medical and psychiatric duties, is called on to participate in many civic and educational duties. For instance, he is asked to participate on panels, make speeches, appear on programs of various types, and to help in planning these programs. This may be ego satisfying since he now is an authority in the community although a certain amount of humility will never do him any harm. He, of course, will wind up doing

school examinations on problem children, work with local law enforcement authorities, alcoholics and their programs, and many charity groups. This tremendous drain on his time and energy does not allow much time to devote to cultural and social activities, but, these, too, are very important for, surprisingly enough, patients want their physicians to be well thought of in the community. The difficulty in socializing with patients in psychotherapy is well known and, of course, is to be avoided.

However, something else can happen in a small community that many times lends itself to important analytical work with the patient in therapy. I, for instance, have had more than one patient indicate that he was glad to know that his therapist was human and liked to enjoy himself occasionally. Various patients, because of the stigma of treatment in a small town, want to be ignored when they are seen publicly by the therapist while other patients, either in an attempt to dilute therapy or in trying to curry favor or be part of the new fad that is developing, want to be recognized socially. Again, these things may lead to very important therapeutic work.

The care of the mental health of any community falls into one of four large categories. I am sure that these categories are the same that occur in a city or a larger community, but they seem to stand out in bolder relief in the small community. The first of these is handling the "cold patch" cases—the chronically debilitated individuals who need immediate supportive care but cannot be expected to be "cured" for any prolonged length of time. These are what I call the malignancies of psychiatry, and the alleviation of immediate mental pain and suffering in the patient as well as the family is the therapeutic goal. A considerable amount of this cold patch treatment must be done if you are the only psychiatrist in the area.

The second category of patients in treatment are those requiring long range care. It most frequently is a psychotherapeutic endeavor which may not bear fruit for many months or even years. This can be very discouraging to people who expect magic. It frequently takes a lot of educating. This has occurred to me twice with local people wanting to develop a mental health clinic. Their feeling was that this wonderful new clinic would cure all the mental ills of the community including delinquency, addiction, marital problems, and other psychiatric illnesses the minute the door opened. Once these people understood that a mental health clinic had several goals for care of the community they were able to see also that just opening the doors of such a building does not necessarily mean that the problem is solved. They become allies and helpers rather than star gazers and do gooders.

A third category is the preventive aspect of mental illness with all its implications for the future and the development of better methods of treatment.

The fourth closely related category has to do with an educational program to help the community understand the what, how, and why of mental illness, thereby again removing much of the stigma attached to mental illness. These categories, of course, overlap greatly. It is the responsibility and the pleasure, actually, of the psychiatrist in a small community to implement these various procedures for his community, something again that his colleague in the larger city may have difficulty doing because of the bulky administrative problem that ensues in the large community.

Now, what are the therapeutic tools necessary if the psychiatrist would take care of the community's emotional needs?? The backbone of his treatment must start with a thorough training and experience in general psychiatry. There will be patients who need and should have the benefit of analysis. There will be other patients who will need long term psychotherapy. Other patients, who are intellectually unable to understand therapy, will need supportive care only. Good training in dynamic psychiatry is imperative with adequate control and supervision with both long and short term patients and the handling of these patients. It is very important, I repeat, that the psychiatrist be well enough trained to recognize and set goals in treatment. His own analysis is im-

portant and helpful whenever possible. Adequate and proper handling of marital problems and the problems in forensic psychiatry that arise must be part of the background and training. It is very difficult to be a "talking doctor" only, so that the armamentarium is not complete unless the psychiatrist has a good background in the physical therapies such as electroconvulsive treatment, insulin treatment, metrazol, and combinations of these treatments. The shock treatments should be learned thoroughly with sufficient duration and rotation through an intensive treatment unit to be able to follow various types of patients. It is imperative also that the psychiatrist know when not to treat. Keeping pace with new drugs and new developments is of utmost importance so that refresher courses and meetings become necessities. Training in neurology, neuroanatomy, forensic psychiatry, and experience enough to know when to refer a patient for possible lobotomy are very important. A working knowledge of electroencephalography many times comes in handy in diagnosing and handling convulsive problems and differentiating these from hysterical or other psychiatric pictures. Many times, the patient is referred with a psychiatric history only to wind up having a brain tumor, central nervous system infection, or some traumatic difficulty that will need diagnosis and treatment.

Economics of practice in a small community is very important. The fact that many patients may be treated with ambulatory shock treatment I believe is something that we have forgotten. While it is convenient to have the patient in a hospital, many times, because of the financial burden and because the family had rather take care of the patinet themselves this financial burden can be relieved by treating the patient on an outpatient basis. I think it is wise always to start treatment in a hospital setting, and as soon as the patient is able to be home he should be treated on an ambulatory basis. It is a well known fact that if the patient cannot pay the large hospital bill he will certainly not have money to pay the physician. Preceding all this, a psychiatrist should have a good background in general medicine. The new residency program set up jointly by the American Psychiatric Association and the National Mental Health Association to train general practitioners in psychiatry will probably do more to foster good general psychiatry than anything else that has occurred in the past ten years.

Obviously no one person can have so much information at his fingertips at all times so that the psychiatrist should have as part of his team, well trained people who can help him. I think, too, it is preferable that at least two psychiatrists work together in any community. This can be a stimulating situation for both of them as well as relieving some of the pressure of the inevitable rapid development of the practice. There is little doubt that psychiatrists are in a "seller's market," and as long as they are willing to do work and see people they will be extremely busy. The isolation of a solo practice is one of the drawbacks. A good clinical psychologist, I feel, is a must as part of the team. He helps in the diagnosing of cases. He helps in doing organic studies and if adequately trained can do an excellent job in counseling and psychotherapy. Despite the arguments frequently heard against the use of clinical psychologists, I find that my associations have been fruitful. It may be that I have been blessed with an unusually good psychologist. As to the argument that a psychologist does not know clinical medicine, I feel that this is something that the psychologist knows himself and does not want to treat patients who have not been cleared or screened as to physical illnesses. The psychologist or psychiatrist who starts treatment without organic studies is not being fair to himself or the patient. Working in a small community is a psychiatrically stimulating and interesting situation, and possibly this going back to the hinterlands where we are needed may drive a wedge into the socialism which we see developing throughout the country.

Abilene, Texas.

The Gorham Proverbs Test

P. O. O'REILLY, M.B., B.CH., and K. HARRISON, PH.D.

For some time the authors have been concerned with the development of a battery of objective tests for the screening of psychiatric cases. Two of these tests (Objective Rorschach[5] and Pfister Colored Pyramid[6]) have been reported. More recently the test battery was extended by the inclusion of Gorham's Proverbs Test,[2] which seemed to offer a useful objective measure of abstraction impairment. This test has both an individual clinical form and a multiple-choice form capable of group administration and clerical scoring. According to its author both forms of the test in a controlled experiment differentiated normals from chronic schizophrenics and organics at the .001 level of confidence on the abstract score, but not the schizophrenics from the organics. He also found that the concrete score of the multiple-choice form of the test differentiated between the chronic schizophrenic and organic groups at the .001 level of confidence.

It is the purpose of this paper to report the results of our use of the multiple-choice form of this test on an individual basis as part of the test battery administered to consecutive admissions to a mental hospital.

Description of the Test

The test was presented in standard form and consisted of 40 items with four answers each. It was scored by stencil. An abstract (Ab) score consisted of the total number of correct responses. A concrete (Co) score consisted of the number of items marked from 18 "concrete" answers. The patients were given a booklet containing proverbs with the following instructions. "Below are some proverbs and you are to indicate what they mean. Black in below the letter on the answer sheet which is the best answer to each proverb; the one which best explains what the proverb means." When the test was completed Ab and Co scores were obtained for each patient. The test was presented on an individual basis and was part of an objective test battery.

From Saskatchewan Hospital, North Battleford, Saskatchewan, Canada.

Subjects

The subjects comprised 67 consecutive admissions to the Saskatchewan Hospital, North Battleford. Diagnosis was made by the clinical staff of the hospital in conference. The research staff were unaware of the clinical diagnosis given on any case until the testing was completed. The group consisted of 30 schizophrenics, 14 other psychotics, 11 psychoneurotics, and 12 of miscellaneous diagnosis. Specifically, the other psychotic subgroup consisted of six manic depressive, one hypomanic, four involutional melancholia, one alcoholic psychosis, one epilepsy with psychosis and one psychosis secondary to cerebral emboli. The miscellaneous subgroup was composed of six patients with a diagnosis of chronic alcoholism and six pathological personalities.

Results

Taking into consideration the smallness of their size the four subgroups (schizophrenics, other psychotics, psychoneurotics, and miscellaneous) statistically showed no significant differentiation on age and intelli-

TABLE I

Comparison of Subgroups' Mean Proverbs Test Scores

	Abstract Scores		Concrete Scores	
Subgroups	Difference Between Means	t	Difference Between Means	t
Schiz/Other Psychotics	2.3	1.57	0.5	.51
Schiz/Psychoneurotics	1.4	.51	0.09	.08
Schiz/Miscellaneous	0.9	.35	1.58	1.61
Other Psychotics/Psychoneurotics	0.9	.27	0.41	.25
Other Psychotics/Miscellaneous	3.2	1.07	1.08	.77
Psychoneurotics/Miscellaneous	2.3	.68	1.49	.89

gence and were regarded as comparable for the purpose of an analysis of the test results.

The means and standard deviations of the abstract and concrete scores of the different subgroups were calculated and the "t" test was applied to see if there was any significance in the variations. No significant difference was found between the means of the different subgroups.

Gorham established cutting points and norms for use with the proverbs test based on intelligence groups arranged according to scores on the word knowledge test of the A. F. Airman Classification Battery.[3] Such treatment of the data was necessitated by the high correlation between intellectual level and performance on the proverbs test.

These cutting points have been applied to intellectual levels on the Wechsler-Bellevue intelligence scale, Form 1 comparable to Gorham's on the word knowledge test and roughly equivalent to the upper quartile, middle half and lower quartile in a distribution of normal subjects, and their usefulness for diagnostic purposes has been examined. The scores of 16 normals all of whom except one are of high intelligence, are also shown for comparison.

It is seen from Table II that although the use of these cutting points correctly places 14 of the 16 normals (87.5%) in the normal range it shows poor discrimination with the psychiatric subgroups. It also places in the normal range 17 of the 30 schizophrenics (57%), six of the 14 other psychotics (43%), seven of the 11 psychoneurotics (64%) and six of the 12 in the miscellaneous subgroup (50%).

Gorham also gives clinical norms for the multiple-choice form of the test based on percentiles derived from the abstract and concrete scores of his normals and chronic schizophrenics, and not taking into consideration intellectual status.[2]

Comparing the scores of our patients on the norms for abstract scores shows that 73 per cent have scores below the median score of the normals (Table III), and 68.5 per cent have scores above the median score of the chronic schizophrenics (Table IV); and of the norms for Concrete Scores 71.5 per cent have scores below the median score of the normals (Table V), and 65 per cent have scores above the median score of the chronic schizophrenics (Table VI).

Although the patients generally score lower abstract and higher concrete scores than Gorham's normal sample they show a wide scatter in all subgroups and the norms give insufficient discrimination for the raw scores of the multiple-choice version of the test to be used for diagnostic screening.

TABLE II

Application of Gorham's Cutting Points to Scores of Various Subgroups

	Normals	Schizophrenics	Other Psychotics	Psychoneurotics	Miscellaneous
HIGH INTELLIGENCE					
(W.K.: 7-9 stanines)					
(W-B: I.Q. 111 and over)					
Ab>26 and Co<2	13	2		1	1
Ab<26 and/or Co>2	2	3	3	1	4
MIDDLE INTELLIGENCE					
(W.K.: 4, 5, 6 stanines)					
(W-B: I.Q. 91-110)					
Ab>15 and Co<4	1	5	4	4	3
Ab<15 and/or Co>4		4	4	1	1
LOW INTELLIGENCE					
(W.K.: 1-3 stanines)					
Ab>12		10	2	2	2
Ab<12		6	1	2	1
Combined Subgroups					
Predicted Classification					
Normal range	14	17	6	7	6
Schizophrenic range	2	13	8	4	6
	16	30	14	11	12

TABLE III

Distribution of Subgroups' Abstract Scores Compared with Normals on the Clinical Norms

	Normals	Admissions to Mental Hospital						
Abstract Percentiles	Percent	Schizophrenics	Other Psychotics	Psychoneurotics	Miscellaneous	All Patients	Percent	
95th and over	5	1	0	0	0	1	1.5)	
75th to 95th	20	1	1	2	0	4	6.0)	27
50th to 75th	25	6	2	1	4	13	19.5)	
25th to 50th	25	9	3	1	5	18	27.0)	
5th to 25th	20	10	6	5	1	22	33.0)	73
Below 5th	5	3	2	2	2	9	13.0)	
	N 30	14	11	12	67	100.0		

TABLE IV

Distribution of Subgroups' Abstract Scores Compared with Chronic Schizophrenics on the Clinical Norms

	Chronic Schizophrenics	Admissions to Mental Hospital						
		Admissions to Mental Hospital						
Abstract Percentiles	Percent	Schizophrenics	Other Psychotics	Psychoneurotics	Miscellaneous	All Patients	Percent	
95th and over	5	1	1	1	0	3	4.5)	
75th to 95th	20	10	2	2	5	19	28.0)	68.5
50th to 75th	25	11	4	4	5	24	36.0)	
25th to 50th	25	5	5	2	1	13	19.0)	
5th to 25th	20	2	1	2	0	5	8.0)	31.5
Below 5th	5	1	1	0	1	3	4.5)	
	N	30	14	11	12	67	100.0	

TABLE V

Distribution of Subgroups' Concrete Scores Compared with Normals on the Clinical Norms

	Normals	Admissions to Mental Hospital						
		Admissions to Mental Hospital						
Concrete Percentiles	Percent	Schizophrenics	Other Psychotics	Psychoneurotics	Miscellaneous	All Patients	Percent	
95th and over							)	
75th to 95th							)	28.5
50th to 75th	50	4	5	4	6	19	)	
25th to 50th	25	6	1	0	3	10	15.0)	
5th to 25th	20	18	7	6	2	33	49.0)	71.5
Below 5th	5	2	1	1	1	5	7.5)	
	N	30	14	11	12	67	100.0	

TABLE VI

Distribution of Subgroups' Concrete Scores Compared with Chronic Schizophrenics on the Clinical Norms

	Chronic Schizophrenics	Admissions to Mental Hospital						
		Admissions to Mental Hospital						
Concrete Percentiles	Percent	Schizophrenics	Other Psychotics	Psychoneurotics	Miscellaneous	All Patients	Percent	
95th and over	5	3	3	2	4	12	18.0)	
75th to 95th	20	7	3	2	5	17	25.0)	65
50th to 75th	25	8	4	2	1	15	22.0)	
25th to 50th	25	10	3	4	1	18	27.0)	
5th to 25th	20	1	0	1	0	2	3.0)	35
Below 5th	5	1	1	0	1	3	5.0)	
	N	30	14	11	12	67	100.0	

Product moment correlations were calculated for both the proverbs abstract and concrete scores with each other and with various Wechsler-Bellevue intelligence test assessments.

The high negative correlation between the abstract and concrete scores supports Gorham's contention that his test measures two opposite aspects of the same intellectual process[1] (Table VII). His finding that abstract scores on the test correlate highly and positively with vocabulary also is supported.[4]

Two estimations of personality integration, the verbal variability index and the performance variability index were derived. The verbal variability index was obtained by averaging the deviations of the verbal subtests from the verbal mean and dividing by the verbal mean. Performance variability index was obtained in like manner using the scores and means of the performance subtests. Rank difference correlations between the ab-

TABLE VII

Intercorrelations of Proverbs Abstract and Concrete Scores with Various W-B Test Assessments

	Proverbs Concrete Score	W-B Full Scale I.Q.	W-B Verbal I.Q.	W-B Performance I.Q.	Comprehension	Similarities	Vocabulary
Proverbs Abstract Score	–.716	.688	.540	.482	.582	.327	.730
Proverbs Concrete		_.222	–.519	–.293	–.470	–.444	–.482
Concrete Score		–.222	–.519	–.293	–.470	–.444	_.482

TABLE VIII

Rank Difference Correlations of Subgroups' Abstract Scores and Various W-B Test Scores

Subgroup	N	Vocabulary	Comprehension	Similarities	Verbal Variability Index	Performance Variability Index
Schizophrenics	29	.801	.486	.6$4	–.352	–.552
Other Psychotics	14	.740	.725	.667	–.409	–.471
Psychoneurotics	11	.839	.786	.651	.093	–.580
Miscellaneous	12	.710	.525	.439	–.161	–.054

stract scores and between these and other Wechsler-Bellevue assessments were calculated (Table VIII). Comparing the subgroups, all show a high positive relationship between their abstract scores and scores on the various verbal tests, but the rather lower correlations of the schizophrenics with comprehension, and of the miscellaneous subgroup with both comprehension and similarities scores were noted.

Also it is of interest to note the negative correlations between the indices of integration and the abstract scores. The results show some measure of relationship in the cases of all psychotics on both verbal and performance indices, and for the psychoneurotics on the performance index only. The more integrated patients showing more even patterns on the Wechsler-Bellevue intelligence scale tend to have higher abstract scores on the Gorham proverbs test.

Discussion

According to the results of this study the multiple-choice form of the Gorham proverbs test, administered individually as part of an objective test battery, failed to differentiate between the various diagnostic categories of mental hospital patients on admission.

High correlations with vocabulary and other Wechsler-Bellevue scores seem to indicate that the test is heavily loaded with 'g' and 'v' factors, although no factor analysis was carried out.

Negative correlations with the indices of integration suggests that the test is capable of measuring impairment in verbal conceptualization, although not with sufficient precision for its use as a sole objective method of differentiating schizophrenics from other categories of mental hospital patients.

Summary

The multiple-choice form of Gorham's proverbs test was administered individually to 67 patients on admission to a mental hospital.

No significant differences were found between the various diagnostic subgroups on the abstract and concrete scores of the test, and Gorham's suggested norms showed poor predictive value.

Correlations between proverbs test scores and various assessments on the Wechsler-Bellevue Intelligence Scale corroborated Gorham's statements about the strong intellectual and verbal elements in the test, and suggested that the test had some limited ability in measuring impairment in verbal conceptualization.

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The Quiet Hysteric and his Captive Respondent

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The official Diagnostic and Statistical Manual[2] has deleted the term hysteria and replaced it with "dissociative and conversion" reaction, two conventionally accepted defense mechanisms derived from the study of hysteria itself. While such caution may be regarded as a minor act of repressive ingratitude toward an illness to which psychiatry owes so much, it also fails to give direction for further inquiry into a syndrome which rather obviously still surrounds us. Moreover, the manual also no longer provides us with a niche for what used to be called the "hysterical personality." Most every teacher of psychiatry may at one time or another have regretted such absence of diagnostic parking space.

Chodoff and Lyons,[1] in a recent paper, have drawn critical attention to such an omission. They have attempted to correlate hysterical symptomatology with the hysterical character and agree with those authors who conclude that hysterical characters do not necessarily develop hysterical symptoms while the latter should remain doubtful evidence of the existence of a hysterical character structure. They then elaborate on a number of attitudinal and character traits at which they arrived by a quantitative, semantic consensus of prominent writers on this subject. These traits they consider as being typical for the clinical picture of a "hysterical personality." Yet, as they doubt whether psychopathological patterns are sufficiently reliable for diagnostic purposes, they propose a set of characteristics which seem almost wholly "symptomatic" of what they later on concede to be possible cultural artefacts.

This communication would like to endorse their request for renewed recognition of a "hysterical character." However, one may question their effort to separate character structure from symptomatology, especially when—toward the end of their paper—the authors themselves point to the "relativity of neurosis and personality disorder." Objections to their approach may be raised on the basis of methodology, logical definition and clinical experience. Therefore, attention to an additional, and perhaps more basic characteristic of the hysterical personality, represents an attempt to re-connect these syndromes. It is notable that Chodoff and Lyons fail to refer to verbal communication patterns of hysterical personalities though many authors, and probably most every clinician, seem impressed with vagueness, generalization and evasiveness in the hysteric's speech. Farber[3] expressed the thought of a peculiar form of communicative disability which not only accounts for continuous interpersonal psychopathology but can be indicative of earliest life experiences during which the modes of communication determine the character of ensuing relationships. This seems in agreement with observations of Marmor, Millar and Ruesch.

Marmor,[5] from the psychoanalytical point of view, relegates a development of the hysterical character to the oral phase of psychosexual development and explains preponderance in females on a socio-cultural basis. Millar,[6] in viewing hysteria as a "failure of hierarchical integration of the central nervous system," states that "reactions to events persist on a more infantile level. It is not that the hysteric has learned more control over his visceral functions (as a fakir might) but that he has never learned anything else. He persists in operating on a non-verbal level. The immature hysteric does not perceive events as does the mature person—as events overlaid in their immediacy by the reverberations of past *organized* experiences, modifying the present and in turn being modified by it. He perceives events as isolated experiences."

Read before the meeting of the Western Division of the American Psychiatric Association, Seattle, Washington, September 24-25, 1959.

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Finally, Ruesch,[7] as a social psychiatrist, observes that the hysterical personality seems to "coordinate word and action in a peculiar way. When transmitting messages he does one thing and says another with the emphasis being on action rather than word." However, in perceiving, he supposedly pays Though Ruesch still calls the hysterical character a "demonstrative personality" and thus remains in line with Chodoff's and Lyon's description, his emphasis on nonverbal versus verbal modes of expression suggests an earlier and therefore more decisive mode of character formation.

Prodded by cultural demands, the hysteric may appear demonstrative, yet in daily diagnostic and therapeutic experience he may also show himself to be a master of understatement, so reminiscent of a Hollywood director's remark "you overact your underacting." The person thus appears infantile rather than demonstrative. If such notoriety be translated into terms of communication, we may label the hysteric's communicative modes as being imprecise, devoid of true conceptualization of feeling and unable to provide unequivocal cues for the respondent. The hysteric cannot talk to himself with any degree of precision, and therefore he must remain utterly vague and noncommittal in contact with others. The numerous, well known patterns to which he must resort could perhaps be best summarized as externalization. By comparison with the schizoid personality, the hysteric certainly seems unaware of his inner self. It then follows that such imprecision, such noncommittal and equivocal initiation of communication will bear results that may range from noncomprehension and ridicule to paranoia in the respondent, who has to guess meaning and interpret clues on premises of his own. Imprecision in verbal expression on the basis of lacking emotional concept formation can thus be considered one of the characteristics of the hysterical personality.

In order to illustrate some of the consequences of such communicative deficits, reference is made to observations of symbiotic neurotic interaction with a hysterical personality, to psychotherapeutic practice and to the vagaries in medical diagnosis. It is difficult, to say the least, to describe a verbal deficit in words. However, the following excerpt may elucidate emotional responses to noncommittal, ambiguous and outright defective types of hysterical communication as they are not infrequently encountered in psychiatric practice:

A rather sophisticated, middle-aged man sought help for depressiveness and reactive alcoholism. He had no history of prior psychiatric disability. The precipitating situation seemed to be his love affair with a woman who was pictured by him as quiet, gentle, accepting and understanding. During the course of treatment, he bitterly complained about his partner's inability to "communicate." Whatever the merits of his complaint, it was evident that a profound misunderstanding had arisen on a verbal level. "When we were together," he said, "she would not talk; I had to provide the clues. When she was away she would not write and when she did her letters seemed meaningless. I bored into each word. I tried to give it meaning. I phoned her, yet again I did all of the talking myself while the telephone company got rich." He then described a mode of communication which seemed almost wholly unilateral; he had to guess her thoughts, her moods, her complaints and her preferences while her answers remained always on a level of "perhaps," "some" and "sort of" to the point where the man went into groundless paranoid ruminations, used stimulants and sedatives indiscriminately. Yet with stubborn persistency he pursued signals he could never decipher and in spite of being aware of his utter frustration he could not desist from following her only to find her in what appeared a situation of infidelity. It is of interest how he described her response to this "surprise." She remained sufficiently vague and by actually not committing herself at all she neither dispelled his doubts nor did she distract in any measure from his faith in her. When their conversations were closely examined it became apparent that she could neither explain nor define her actions and she succeeded in initiating another series of ruminative excuses and self accusations in the patient. Although the woman never had made specific accusations nor inferences, the patient said that he felt continuously on the defensive yet never really knew why he should apologize. On the other hand, he continued to provide clues for explaining and defending himself.

This failure to comprehend her can be gauged by an example of interchange during therapy. The therapist questioned his reasons for trying to resume the lengthily precarious relationship and inquired, "Why do you want to contact her again? Do you want her to forgive you?" The patient com-

pletely misunderstood the irony of the remark and gave a number of reasons for which he should have asked her forgiveness. Later on, the woman contacted the therapist on her own since she intended to marry the patient. She had become upset by his more and more suspicious and irrational behavior. It turned out that she had undergone psychotherapy previously for phobic symptoms and that a previous marriage and a lengthy affair with another man had both resulted in similar behavior patterns on the side of her lovers. Each one had reacted with drinking, exhibited paranoid symptomatology and as far as could be learned, both had reverted to reasonable stability following separation from her. She related that her own psychotherapy had been a failure inasmuch as her therapist "had been unable to make her talk." To the examiner, vagueness, lack of commitment, generalization and imprecision in her communication were most conspicuous while a longitudinal history revealed almost all of the occurrences, symptoms and reactions which one so commonly associates with a hysterical character structure.

If one views paranoid thinking as an autistic response to ambiguous clues, the hysteric's capacity to mobilize a paranoid potential in her partner is neither novel nor surprising.

For the sake of demonstration, only those aspects of the symbiotic psychopathology were mentioned which referred to verbal behavior. Emphasis has been placed on communication which precipitates and perpetuates neurotic longings. The most striking feature seems to be that the less expressive, the more vague and indefinite communicator can succeed in assuming almost complete control over an insightful and perhaps even more versatile partner. It looks as if the respondent finds himself in a situation in which he must continuously "force out" of the nonverbal person exactness, preciseness and commitment. However, no urgency applied, no variant exacted, no clue extended, will elicit responses or extricate the captive communicator. Ruesch believes that hysterical personalities benefit from psychotherapy "when a therapist helps them to integrate the nonverbal with the verbal." This raises a crucial question of technique. While free association is rather glibly achieved by the demonstrative variety of the hysterical character, it does not easily come about in the impoverished communicator who must shy away from spontaneity and early material. The "focal communication concept" as proposed by Greenhill[4] may offer earlier inroads. With his technique of focus on a current conflict, a more precise conceptualization seems possible. Configurations of the present remain of symbolic significance while being more readily available for reality testing and the therapist's pressure for elaboration.

Psychotherapeutic experience with hysterics leads one to speculate that this verbal communicative deficit may be regarded as their primary difficulty. For, whenever one deals intensively with those hysterical personalities which correspond to the clinical criteria proposed by Chodoff and Lyons, it rapidly appears that all symptoms denoting overemphasis and histrionicity sooner or later fall by the wayside as the patient experiences his inability to convey true meaning to the therapist and to himself. Sequentially, this is often followed by the emergence of numerous symptoms denoting action taking, somatic complaints or outright conversions. All of these seem then to be superficial attempts to ward off anxiety that arises whenever the patient is confronted with his inability to conceptualize feelings.

Another, though by no means the last, troublesome area of the effects of communicative imprecision is encountered in general medical diagnosis. One is only too often called upon for consultation during medical hospitalizations when the actual diagnostic problem did not arise with the presence of an unusual or perplexing illness, but with the patient's complete inability to give a meaningful history. Internists are even more bewildered when they encounter a patient who gives an overdetailed account, thus hardly leaving room for misunderstanding or omission. However, they cannot suspect that such overmeticulousness in description could denote a hysterical rather than obsessive type of informant. The hysteric's speech pattern is often termed as "overtalkative," "over-emphatic in detail" and then assigned to an obsessive-compulsive overlay. From the vantage point of communication this may be regarded as an elabora-

tion on the original shortcoming and if approached with closer scrutiny, it represents pseudo-precise communication rather than actual transmission of feeling. In this connection, it also my be stated that the specific verbal deficit of the hysteric is only superficially ameliorated and accessible to conventional education and seems completely independent of the level of intelligence. Moreover, by its very nature of inaccuracy in the transmission of meaning, it becomes self-perpetuating and will lead to difficulties in almost all relationships.

One wonders about the genesis of such verbal ineptitude, since in the field of communication and ensuing relationships it is often difficult to distinguish cause from effect. One may correlate verbal imprecision with conventional theories of libidinal arrest or fixation. But it is also conspicuous how frequently a patient has identified with an important parental figure who shows similar verbal deficits. Could it then be assumed that this lack of inner self assessment is acquired by contiguity and contact rather than in the sense of a primary defense against anxiety in interaction with the parent? Marmor remarks on a close psychodynamic relationship between hysteria and schizophrenia. He relegates the eventual outcome to differences in ego development. Millar does not specify his concept about the nature of a learning process in his interpretation of hysteria. Both explanations seem to be psychogenetic in character and rest on the ground of acquired behavior. Personal, clinical experience suggests that conversions, dissociations and displacements are more freely encountered in patients who—though psychodiagnostically found to be hysterical personalities—are in their overt behavior and appearance remarkable for the absence of those criteria associated with histrionicity and extroversion. However, if one pays closer attention to their communicative disability, to their failure to conceptualize feelings and to express these in meaningful language, one will find that an exterior facade of quietness and unassuming orderliness conceals the potential of a hysterical personality. Thus, on the basis of communicative patterns, the "quiet hysteric" may represent the nosological link between hysterical symptomatology and the hysterical character.

Summary and Conclusions

The substitution of the diagnostic term hysteria by two hypothetical defense mechanisms is considered to be of doubtful advantage. Changes in etymological meaning probably reflect shifts in cultural settings rather than altered psychiatric perspectives of an illness which has occupied a prominent position throughout the ages. The contemporary attempts to dissociate hysterical symptomatology from a hysterical personality may be a further obstacle in clarification of the syndrome. On the other hand, attention to communication as a prerequisite for relationships suggests the existence of a verbal deficit which may be typical for the hysterical character. An attempt is made to describe this deficit and to arrive at the formulation of the "silent" or "quiet" type of a hysteric. This variant may be more liable to react with the classical symptoms while the traditional histrionic variety remains less encumbered by virtue of action taking. Recognition of a specific verbal deficit as an additional characteristic of the hysteric may provide a nosologic link between symptomatology and the traditional concept of a hysterical personality.

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A Time Limited Clinical Evaluation of Phenelzine in the Treatment of Endogenous Depressions

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Purpose

In view of the importance of the cost of hospitalization, time away from work, business, or profession, and time away from home for mothers as well as the exhausting and debilitating effect of endogenous depression, this study was designed to determine the therapeutic effectiveness of phenelzine over a period of time not to exceed two weeks. Those patients showing evidence of improvement within the two week period were to be continued on phenelzine, while those without definite improvement were to be discontinued and considered for other therapeutic approaches. This study was conducted in an active treatment center with 42.6% of the subjects representing private patients and 57.4% representing part pay staff patients in whom cost and time are urgently important considerations as contrasted with patients that may be admitted to the Veterans Administration or State Hospitals.

Criteria for Diagnosis of Depression

1) Diurnal variation of symptoms with early morning intensification of symptoms.

2) Terminal sleep disturbance or the lack of satisfactory rest from sleep.

3) Excessive worry about trivials, overconcern with everyday problems, indecisiveness, undue concern with health and bodily functions, feelings of uncertainty with increased worry over future security.

4) Persistent or progressive isolated or multiple somatic complaints with negative or insignificant physical findings.

5) A change in disposition characterized by a loss or impairment of confidence, ambition, former interests in general, libido, appetite and unwarranted feelings of shame, incompetence and guilt.

6) Past personal history of a previously healthy well-adjusted person who has undergone the above changes.

7) Past medical history often demonstrating a similar episode or episodes.

8) Onset of symptoms after age 30 in a previously well adjusted personality precluding a diagnosis of psychoneurosis.

Results

Our study comprised 112 patients suffering with endogenous depressions who were all treated with phenelzine, 15 mg. three times per day; 45 patients (40.2%) responded with definite improvement during the 14 day period. There was a decrease in the diurnal variation of mood, a sustained sleep pattern appeared, over concern and worry decreased, disposition improved and somatic complaints decreased within the two week period.

A somewhat surprising and very gratifying result was found in the treatment of a small group of patients with obsessive-compulsive neuroses. Six of seven such patients experienced definite improvement in less than two weeks of treatment. In addition to their obsessive-compulsive neuroses, four patients had had recurrent episodes of depression. One of those who responded well had previously had an unsuccessful minimal bi-median pre-frontal lobotomy.

Six patients with a diagnosis of anxiety psychoneurosis with depressive features were given phenelzine, 15 mg. three times a day, with three displaying definite improvement within fourteen days.

Three schizo-affective (depressed) disorders were given phenelzine, 15 mg. three times a day with none demonstrating improvement within fourteen days.

Laboratory Studies

A liver profile, consisting of alkaline phos-

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Phenalzine was supplied as Nardil by Warner Chilcott Laboratories.

This study supported by a grant from Warner Chilcott Laboratories, Morris Plains, N. J.

phatase, S.G.O.T., qualitative urinary bilirubin and serum bilirubin, were carried out on 31% of the patients who had been taking phenelzine over a period of one to four months. There was no laboratory evidence of impaired liver function. In the remainder of the patients, there was no clinically observable evidence of hepato-renal dysfunction during the administration of phenelzine.

Side Effects

Postural Hypotension: Seven patients complained of severe dizziness and six (4%) were found to have definite postural hypotension. The seventh patient had no clinical evidence of postural hypotension. The symptoms disappeared in three to four days after discontinuing phenelzine in five cases and after decreasing the dosage by 15 mg. per day in two cases.

Restlessness: Five patients (3.1%) complained of severe restlessness and agitation after taking phenelzine from seven to 70 days. The symptoms subsided within three to four days in three patients when phenelzine was discontinued and in two patients when phenelzine was decreased by 15 mg. per day.

Detachment: Two patients (1.5%) complained of feeling "detached" or "being in a void" within seven days after initiating phenelzine therapy. The symptoms disappeared in three days after discontinuing phenelzine in one patient and decreasing the dosage by 15 mg. in the other patient.

Excitement: Three patients (2.3%), all suffering from depressions, developed a pathologic state of excitement requiring treatment while under phenelzine therapy. One of these patients, who had suffered from previous manic episodes, displayed a striking mood change within 43 hours after beginning phenelzine therapy. The other two patients, with no history of previous episodes of manic excitement, displayed such changes only after several months of phenelzine therapy. Whether these striking mood changes are a result primarily of medication or coincidental are questions for further investigation.

Rash: One patient (0.7%), receiving only phenelzine, developed a generalized pruritic erythematous morbilliform rash within five days of initiating phenelzine therapy. Phenelzine was discontinued and Benadryl 50 mg. four times per day was administered. The rash disappeared after ten days and phenelzine was again initiated three days later without recurrence of the rash.

Glaucoma: One patient (0.7%) with borderline elevated eye pressures and a severe endogenous depression was started on phenelzine, 15 mg. three times per day. After 95 days of therapy she developed absolute glaucoma pressure readings in both eyes. Phenelzine was decreased to 15 mg. per day and the pressure returned to its formal level within 16 days.

Summary

A therapeutic trial with phenelzine for two weeks was given to 128 patients; 40.2% of 112 patients suffering from indogenous depressions were improved within this two-week period. A surprising observation was that six of seven patients with chronic obsessive-compulsive states were definitely improved. There was neither laboratory nor clinically observable evidence of hepatic involvement. This study is not comparable to a long term study of the clinical effectiveness of this drug, however, the early improvement with phenelzine is demonstrated where time and financial considerations are important to the patient suffering from endogenous depression.

Kevadon: A New, Safe, Sleep-Inducing Agent

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Kevadon* (thalidomide) is alpha (N-phthalimido) glutarimide. It is completely different pharmacologically from other agents used to induce sleep. In the reports in foreign literature, this compound has been designated by the code name, "K 17," and by the trademarks, "Contergan," "Softenon," and "Distaval." It is a white crystalline compound with a melting point of 269-271°C. The substance is odorless and tasteless. Since it is not soluble in any of the ordinary vehicles used in the preparation of parenteral solutions, Kevadon has been administered to human beings only by mouth. Sodium carboxymethyl cellulose and gum acacia have been used to prepare suspensions of Kevadon for injection in experimental animals. When given parenterally, Kevadon behaves in animals much as in oral administration.

The pharmacology of Kevadon was first reported by Kunz, Keller, and Mückter[1] who found that the new compound does not put experimental animals to sleep but that it does antagonize the effects of well-known central stimulants on spontaneous activity of rodents in a "jingle cage." However, it was not possible to establish a therapeutic ratio comparing the dose which produces a measurable and potential therapeutic effect either with a minimal lethal dose or with the usual LD_{50} (lethal dose for 50 per cent of the animals) since it was not possible to kill any of the animals by administration of excessive overdoses. The largest dose which it was practical to give by mouth was 5,000 mg./Kg. (equivalent in a 70 Kg. man to a single dose of 350,000 mg., i.e., 350 Gm.—more than three-quarters of a pound. None of the animals so tested died, nor did any die from similar doses injected subcutaneously after suspension in gum acacia. Not only did the animals survive, but actually these massive doses failed to produce any abnormality of cardiovascular or respiratory function. *The animals did not even fall asleep.*

In the first seven clinical papers published on Kevadon,[2-8] there is recorded a total of 940 cases plus an unspecified number of cases in one of the texts.[3] The new drug was usually administered in single doses of 50 mg. or 100 mg. at the hour of sleep to these patients and the vast majority were described as sleeping very well. This suggests that in Kevadon we have a compound which is highly effective in producing sleep in human beings but does not influence respiration, and is so nontoxic that doses large enough to kill an experimental animal either cannot be given or are so large that they will be given only with great difficulty. This makes Kevadon unique.

Salter, Lodge-Patch, and Hare[7] adapted the methodology of Lasagna[9] for studying sleep-induction qualities of a new compound. Each of 24 subjects was observed by a nurse every 30 minutes under each of three conditions. On one occasion thalidomide was administered in single dosage of 50 mg. and on another, in dosage of 100 mg. given at the hour of sleep. The third treatment in this comparative study was a single dose of 200 mg. secobarbital given at the hour of sleep. By recording whether each patient under each condition was awake or asleep and then multiplying by a factor of 30, a number representing "waking minutes" was found for each subject. The mean number of "waking minutes" for the 24 subjects under each of the three conditions of treatment was determined. By these standards, a low number indicates a relatively potent sleep-inducing agent whereas a higher number indicates less potency.

The average time awake for the group on 50 mg. thalidomide was 88 minutes; on 200 mg. secobarbital, 80 minutes; and on 100 mg. thalidomide, only 69 minutes. The superi-

From Lincoln State Hospital, Lincoln, Nebraska.

*Kevadon is the trademark of The Wm. S. Merrell Company, Cincinnati 15, Ohio, for its brand of thalidomide.

ority of 100 mg. thalidomide over 200 mg. secobarbital was statistically significant (t=2.86; p=less than 0.01). The authors concluded that the milligram potency of thalidomide as a sleep-inducing agent was more than two times that of secobarbital but less than four times—about three times.

DeSouza[10] reported that a 70 year old male patient who had been receiving 200 mg thalidomide nightly for insomnia associated with mild senile dementia by error took a single dose of 2,100 mg. He slept for 12 hours and was somewhat more drowsy than usual for the next 24 hours. However, no antidote was needed or given and no respiratory or cardiac depression occurred.

In Jung's series of 300 cases,[5] many patients suffered from chronic liver disease. In no case did thalidomide produce evidence of further damage, nor was there any unusual prolongation of effect of the drug as is sometimes seen when comparable barbiturates are given to such patients. Five were suffering from adrenal insufficiency secondary to long-standing tuberculosis. Thalidomide caused no further change in 17-ketosteroid or corticosteroid excretion. No habituation occurred and there were no withdrawal symptoms when the drug was stopped. On the contrary, in some cases it appeared as if the drug produced a more normal sleep habit so that oftentimes continued therapy was not needed. Greene and Farran[4] found no effect of the drug on thyroid function (radioactive iodine uptake studies); and Stärk[8] confirmed the lack of effect of thalidomide upon basal metabolic rate and respiratory function.

The first group of patients treated by us consisted of 10 adult males and 10 adult females who had been hospitalized at the Lincoln State Hospital for a prolonged period of time. Each was given 200 mg. thalidomide (2 to 4 times the therapeutic dose) at the hour of sleep nightly, from March 7, 1959 until May 23, 1959. Determinations of body weight, hemoglobin, red blood cell count, white blood cell count, differential, urinalysis, B.U.N., B.S.P., and cephalin flocculation were all done before and after the test period. The findings show that continued administration of Kevadon in several times the therapeutic dose produced no evidence of harm to the measurable functions of the vital organs.

Following the test period the dose was adjusted individually and each of the 20 patients received from 100 mg. to 400 mg. Kevadon nightly. The dose was adjusted to produce the most restful night possible for each of these disturbed, psychotic patients. No side effects were encountered. At the end of six months of treatment the medication was stopped abruptly and no manifestations of withdrawal occurred. Addiction does not seem to be a potential hazard with Kevadon.

Three patients had been receiving amobarbital, 200 mg., nightly. The medication was changed to 100 mg. amobarbital plus 100 mg. of Kevadon. In each case, the patient slept well but was more alert the next morning than he had been when the larger dose of the barbiturate was used alone.

A group of 15 patients was receiving various phenothiazine derivatives or meprobamate. Kevadon was prescribed symptomatically in dosage of 100 mg. at the hour of sleep to control insomnia. Not only did the patients sleep better, but there was a distinct clinical impression that the daytime tranquilizers were more effective when Kevadon was given at night. This potentiating effect of Kevadon on the efficacy of tranquilizers will be the subject of further study and will be reported separately.

We were so encouraged by our experience at the Lincoln State Hospital that we next gave Kevadon to a series of private patients seen in office practice who complained of insomnia secondary to a wide variety of ailments. Except in two patients who had been taking large doses of barbiturates for a long period of time, Kevadon induced sleep much as it had in the institutionalized cases. However, the two patients who had become accustomed to barbiturates required 400 mg. Kevadon, and even in that dose the new drug was not as effective as were previous medications. From this limited experience, it would seem that Kevadon is sufficiently different in its activity that it does not support a potential barbiturate habituation.

Insofar as induction of sleep was con-

cerned, Kevadon in dosage of 100 mg. produced the desired results in seven of the first nine ambulatory patients. However, drowsiness the following morning was reported by six of these nine patients who were given a bedtime dose of 100 mg. Accordingly, the dose was reduced to 50 mg. at the hour of sleep in the next 16 patients. Only two of these complained of drowsiness the next morning and thirteen slept well. Since many people are drowsy in the morning anyway, the significance of this low incidence of "hang-over" seems unimportant. The drug was more efficacious in people who used only an occasional sedative than in those accustomed to the chronic use of barbiturates in relatively high dosage.

When early morning drowsiness occurred it was not corrected by the taking of several cups of strong coffee. It may be that a tolerance to caffeine developed over a long period of time renders coffee virtually useless to correct drug-induced sedation. In those patients who are highly sensitive to Kevadon, reduction of the nightly dose to 50 mg. was a satisfactory way of inducing restful sleep with a minimum of side effects.

Mild constipation is mentioned in the European literature as a potential side effect. This did not occur in our series of 63 patients—hospitalized and ambulatory.

Approximately 25 per cent of the patients admitted to general hospitals for treatment of acute poisoning are suffering from barbiturate intoxication.[11] In a study or recent insurance statistics, barbiturates were reported as the cause of death in six per cent of the suicides and in 18 per cent of the accidental deaths among policy holders.[12] However, it has not yet been possible to kill an experimental animal with large doses of oral Kevadon[1] and survival of a human being following oral administration of a single dose of 2,100 mg. has been reported.[10] It would seem, therefore, that in Kevadon we have a sleep-inducing agent comparable in potency and efficacy with the barbiturates and probably free from danger of serious consequences in the event of gross overdosage.

Summary and Conclusions

Kevadon is a new type of sleep-inducing agent, unrelated chemically to barbiturates and superior to other sleep-inducing agents with respect to potency, efficacy and safety. In experimental animals, it does not induce sleep, produces no respiratory depression, and does not cause death even in huge dosage of 5,000 mg./Kg. In human beings, Kevadon produces no impairment of measurable functions of vital organs even when administered for prolonged periods in several times the therapeutic dosage. It is not habit forming and does not produce withdrawal symptoms when stopped abruptly after six months of administration of several times the therapeutic dose.

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Total Push Therapy with Isocarboxazid

MARJORIE G. MORRISON, M.D., and HENRY A. WEITZ, M.D.

The primary objective of a hospital for the mentally ill is to cure the patients if possible. It is almost as important, particularly in a small institution with a continuous waiting list, to accelerate the rate of improvement and reduce the complexity of treatment. Because of their desire to help more patients in less time, the personnel is receptive to new ideas, methods and medications, including the so-called psychotropic drugs.

In thse situations, the worth of a chemotherapeutic agent is not judged by itself but as part of a healing program involving psychotherapy, occupational and recreational therapy, regular nursing care, electroshock treatments if required, and, in our own case, total push therapy with special attention to the religious welfare of the patients. Because of our special facilities and the rural background of many of our patients, outdoor sports and light garden projects also play an important role in the program.

We have been eager to find the ideal or lacking that the best chemical adjunct to our combined program, and to this end we have made what we considered valid trials of several antidepressant compounds. The latest on this list is isocarboxazid, an amine oxidase inhibitor and analog of iproniazid (Marsilid®, Hoffmann-La Roche Inc.), but reported to be many times more potent[1] and without the toxicity and potentially serious side effects of the latter.[2-4] Because of our relative success with this drug, we felt that the result of our experience would be of both interest and value to others working in similar fields.

Method and Material

Over a period of six months, isocarboxazid was given to 103 emotionally disturbed patients, 84 female and 19 male, in age ranging from 16 to 77 years. At the time treatment was initiated, the patients had been ill for from three months to several years and were variously diagnosed as manic-depressive depressed, undifferentiated chronic schizophrenic with depressive features, paranoid schizophrenic and obsessive-compulsive; 80 were hospitalized and 23 were treated on an out-patient basis. Eight were taken off the medication before completion of treatment for various reasons mentioned below.

The starting dose was 30 mg. daily, reduced to 20 mg. upon improvement and to 10 mg. for maintenance. Length of treatment varied from one month to the entire duration of the study. Previous treatment consisted of the program listed above, often including antidepressants and/or tranquilizers. Adjuvant therapy during this trial was the same, except that isocarboxazid took the place of other antidepressants.

Blood counts and weight were checked on all patients at the beginning of and weekly during the study. Blood pressures were taken weekly on out-patients and daily on in-patients. Liver function tests were performed periodically on the in-patients; these were usually bromsulphalein determinations but also included serum bilirubin, cephalin flocculation, thymol turbidity and the transaminase tests.

It was our opinion that the multiplicity of therapeutic measures made unreliable an accurate "fair to excellent" estimate of the singular effectiveness of isocarboxazid. For this reason we made no attempt to judge the drug's effectiveness by degrees, relying instead on a simple—but significant for the hospital physician—division into "improved" and "unimproved" as evaluated and agreed upon by the authors.

Results

Table I shows our evaluation of isocarboxazid by diagnostic categories among in- and out-patients. It is readily seen that in 86 (83.5 per cent) of the 103 patients the drug definitely contributed to therapy.

The compound, isocarboxazid, used in this study was supplied by Hoffmann-La Roche Inc., Nutley, N. J., under their trademark, Marplan.

From Philhaven Hospital, Lebanon, Pa. (sponsored by the Lancaster, Pa., Mennonite Conference.)

TABLE I

Diagnoses	Improved In-Patients	Improved Out-Patients	Unimproved In-Patients	Unimproved Out-Patients	Totals
Manic - depressive, depressed	58	10	5	3	76
Schizophrenic, chronic undifferentiated with depressive features	9	4	Disc.	Disc.	13
Schizophrenic, paranoid	2	4			2
Obsessive-compulsive	2	1	4	5	12
Totals	71	15	9	8	103
	68.9	14.6	8.7	7.8	100.0
	83.5%		16.5%		

Based on previous experience with patients suffering from similar symptoms, the improvement was evident in four ways:

1. The anticipated hospital stay was reduced by an average of 2 to 4 weeks.

2. Although electroshock where indicated was delayed for one week after discontinuance of the drug (to avoid possible potentiation of pentothal sodium[5]), the anticipated average courses of about 20 treatments were reduced to as low as 3 or 4 in some patients.

3. There was a general improvement in appetite and zest for food, and weight gain in many who were underweight.

4. Patients manifested a greater interest in their environment, including increased and very welcome cooperation in the total push regime, thus further facilitating their recovery or improvement.

In eight of the original 103, isocarboxazid was discontinued before significant therapeutic effects could be noted. Three of these were out-patients who exhibited sufficient agitation in our opinion to warrant discontinuance, although it is conceivable that had they been hospitalized, the effect would have been taken in stride and perhaps disappeared. Four developed hypotension with episodes of syncope and the possible hazards of further medication led to its stoppage. The eighth, a 16-year-old girl, was on 20 units of insulin daily as an appetite stimulant. She had a prolonged insulin reaction and while there was no definite evidence of the prolongation being due to isocarboxazid and no previous reports of hypoglycemia from the drug, it was discontinued as a precautionary measure.

Side effects were temporary or subsided with reduced dosage. These consisted of fairly general mild hypotension, occasional agitation, some constipation (readily managed with laxatives as needed), and one instance of urinary retention. There was no ankle edema, leukopenia or evidence of jaundice. All liver function tests were consistently within normal range.

Case Histories

Case 1: A 52-year-old female had suffered from a recurrent agitated depression for 12 years, with loss of appetite and inability to hold gainful employment. The severity of her illness was such that during one period of depression she set herself on fire and was hospitalized for 10 months for treatment of burns.

Previous unsuccessful treatment included a number of tranquilizers, insulin and several courses of EST. She had two remissions on iproniazid but this was discontinued because of edema and paresthesias.

On February 17, 1959, she was started simultaneously on isocarboxazid 10 mg. t.i.d. and dextro amphetamine sulfate with amobarbital (Dexamyl Spansules, Smith, Kline & French Laboratories, Philadelphia, Pa.). The following are our clinical notes:

February 24: Patient reports almost complete reversal of symptoms.

March 4: Patient doing well. Isocarboxazid Rx cut to 10 mg. A.M. and noon.

March 14: Patient doing well mentally but has bad synovitis of the left knee. Isocarboxazid Rx cut to 10 mg. A.M.

March 25: Patient's mental status good but knee condition seems worse; placed under care of an orthopedic specialist.

June 1: Dextro amphetamine sulfate discontinued; isocarboxazid continued 10 mg. A.M.

October 7: Patient continues to take 10 mg. isocarboxazid daily. She remains in good health. This remission since February has been the longest in 10 years. Although badly handicapped because of a severe multiple sclerosis, patient has obtained part-time work. She is happy; her family is happy; things are going very well. The improvement here is wonderful. Without current medication, we feel this patient would be in a state hospital.

Case 2: A 54-year-old female had a primary diagnosis of Meniére's disease and a resultant depressive reaction. Her illness had persisted in varying degrees of severity for about nine years and she

had been treated with all types of drugs, psychotherapy and EST on several occasions. EST brought about improvement but always with prompt relapse. This occurred one month after the most recent course, with the patient complaining that her head and face felt tight and frozen, her head was pounding and there was a drawing sensation in her neck; she had feelings of nausea and sadness and had no interest in doing anything.

During the EST she had been on dimenhydrinate (Dramamine, G. D. Searle & Co.) and prochlorperazine with isopropamide (Combid Spansules, Smith, Kline & French Laboratories) b.i.d. This Rx was continued and instead of reinstituting EST, isocarboxazid 10 mg. A.M. and noon was added.

Two months later both husband and wife felt that there was an improvement in interest, attitude and outlook and that it was worthwhile to continue the drug. While most of the psychosomatic symptoms remain, the patient seems more able to "make a stand."

This is one of two cases involving Ménière's disease where impressive results were obtained.

Case 3: A 43-year-old female was a somewhat inadequate personality with an agitated depression. In the past seven years she had been given several courses of EST, numerous tranquilizers and an antidepressant amine oxidase inhibitor, phenylethylhydrazine (Nardil, Warner-Chilcott Laboratories).

Treatment with isocarboxazid was instituted. She had been receiving chlorpromazine (Thorazine, Smith, Kline & French Laboratories) 50 mg. q.i.d. for two years but was still "dragging along" with lack of energy, difficulty in sleeping, poor appetite, periodic severe headaches and a feeling of being shut off and isolated from everyone.

Treatment with isocarboxazid 10 mg. A.M. (a small initial dose because of a fairly severe hypotensive reaction to phenylethylhydrazine) was instituted and thioridiazine (Mellaril, Sandoz Pharmaceuticals) 50 mg. q.i.d. was given. One month later the patient reported improvement in sleeping and eating and increased interest in her home and activities outside the home. She is anxious to continue the medications.

Case 4: A 32-year-old married male had a paranoid episode several years previous that was cause for his discharge from the armed services. Recovering from this, he suffered a severe head injury that necessitated surgical implantation of a silver plate in his skull. Six months before he suffered a relapse, became depressed, unable to work and eventually totally incapacitated. Admitted to the hospital, he was diagnosed as a schizophrenic paranoid with strong ideas of homosexuality.

Following three months of therapy, from which EST had to be eliminated because of the head injury, he was started on isocarboxazid. Recovery has been such that the patient can be considered normal in all practical respects including employment. While it seems obvious that total therapy was required in this case, results after instituting isocarboxazid must be called outstanding.

Summary

Of 103 in- and out-patients in a small religiously oriented hospital for the emotionally disturbed, 86 (83.5 per cent) improved on isocarboxazid. Improvement was more gratifying than with other antidepressants and was manifested in a shortening of anticipated hospital residence and EST treatments, increased appetite and weight gain for those who were underweight, and a greater interest in their environment, which for in-patients particularly meant greater cooperation in and effectiveness of total push therapy.

The drug was discontinued in three patients because of agitation, in four because of hypotension and in one for precautionary reasons associated with insulin administration. Other side effects were minor and temporary; there was no edema or leukopenia and liver function tests remained normal.

In our experience isocarboxazid was of real and special value under the conditions prevailing in a small hospital, where space and services are in great demand, in helping to accelerate patient improvement and making the facilities available to more patients in a given period of time.

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New Convulsant Anesthetic Agents

Further Studies of Compounds #22451 and #31777 (Lilly)

EMERICK FRIEDMAN, M.D.

In a recent report[1] the clinical and EEG effects of Compound #22451 were described. The original work[2] on this substance was confirmed; it was found to be a potent and safe ultrashort intravenous anesthetic agent which had analeptic accompaniments. The latter were displayed by brief myoclonic reactions at times, with EEG patterns indicative of convulsant stimulation during anesthesia. The present work elaborates further on these experiences and describes other related experimental developments. The terms "analeptic" and "convulsant" may be inaccurate. "Stimulatory" seems more appropriate.

Compound #22451, as a parent substance, is a mixture of four optically active stereoisomers of 1-methyl-5-(1-methyl-2-pentynyl)-5-allyl-barbituric acid. Pharmacologic studies[3] of these isomers resulted in the identification of the predominantly, or exclusively, anesthetic isomer form of the anesthetic-analeptic isomer. The predominantly anesthetic substance, now known as Brevital (methohexital, Lilly) has been used extensively as an ultrashort acting intravenous anesthetic,[4] possesses no convulsant properties and must not be confused with the other compounds. The anesthetic-analeptic stereoisomer is identified as Compound #31777 and is probably the most powerful barbiturate anesthetic.[3] Its action in animal work, however, produced hyperirritability and myoclonic twitching. It was believed important to investigate the therapeutic potential of Compound #31777 in view of the established background of convulsive therapies. Preliminary clinical and EEG studies using Compound #31777 alone and then combined with Brevital were undertaken. Preliminary studies of the possible therapeutic usefulness of such anesthetic-analeptic agents were also undertaken together with EEG activation studies in certain instances of organic diseases of the brain.

Presented at a meeting of the Eastern Psychiatric Research Association, New York City, Feb. 4, 1960.

Procedure

To elaborate further on the previous reports on Compound #22451, the EEG findings and the immediate clinical effects of this compound are described below. The patients in this study were given 2.0-5.0 cc. of a 1% solution of the compound in distilled water, to which had been added gr. 1/150 atropine sulphate. The solution was injected at the rate of 1.0 cc. per ten seconds. The EEG tracings were taken during the entire period until after awakening. Pulse, blood pressure, and respiratory findings were taken, and clinical observations made. Typical EEG tracings (Fig. 1) show monopolar leads in the standard No. I settings, outlining chiefly frontal and parietal areas. The clinical features are outlined in Table I.

After it was found that Compound #22451 possessed analeptic qualities, and Compound #31777 was identified as the specific stereoisomer that was potently anesthetic-analeptic, the latter compound was examined further in this study. Compound #31777 was administered intravenously in the same concentration and in the same manner as had been done with Compound #22451. It was found within relatively few trials, that 2.0 to 4.0 cc. of Compound #31777 resulted in instantaneous sleep with generalized myoclonic twitchings of mild degree and brief respiratory or pulse changes. Twitchings often preceded sleep or occurred after awakening. It was also noted that the subjective manifestations accompanying such administration were at times unpleasant, or that anesthesia was so brief that patients claimed they had not even been asleep although clinically they obviously were anesthetized for one to four minutes. The previous experi-

EEG Studies with Compound #22451

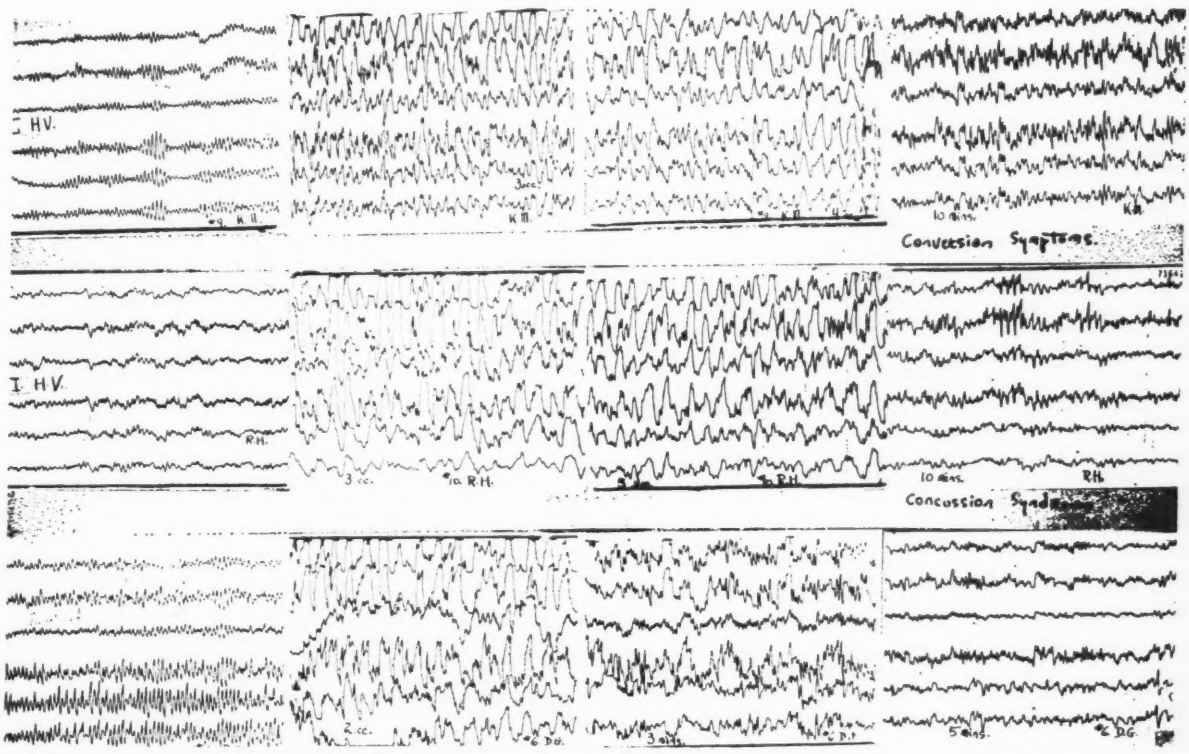

Figure 1. (K.M.)—45-year-old man with years of conversion symptoms referable to the back. At 2.0-3.0 cc., fairly synchronous giant complex waves (3-4/sec.) chiefly in the frontal areas with superimposed spikes. Increase in size of giant slow waves at 4.0 cc. Pattern gradually resolved in ten minutes to an irregular complex slow spiking returning to the resting pattern in less than 20 minutes.

(R.H.)—22-year-old man with moderate post-concussion syndrome approximately three years ago. 2.0-3.0 cc. brought out synchronous bursts of giant complex waves with superimposed and interposed spiking lasting for seven to eight minutes. Pattern returned to normal in less than 15 minutes.

(D.G.)—26-year-old woman with moderate concussion, but chiefly conversion symptoms improving at the time of present examination. At 2.0-3.0 cc. there resulted a continuous burst of giant waves, which gradually assumed complex formation with superimposed and interposed spiking. Complex spike formation in about three minutes. Awakened in five minutes with rare slow spiking for several minutes thereafter.

TABLE I

Clinical EEG Effects

Compound and Amount	Number Trials	Average Pulse Change	Average Respiration Change: Induction	Average Respiration Change: Maintenance	Average Duration of Sleep ** (Minutes)	Av. Duration of Serial Slow Waves/ Spikes (Minutes)	Instances of Myoclonic Twitching
#22451 ..... 2.0-4.0 cc.	20	+24	—6	+8	8	6	1 (5%)
#31777 ..... 2.0-4.0 cc.	30 (10 with EEG)	+26	+8	+8	2–4	3	28 (93%)
Brevital ..... 10.0 cc.	20	+12	—6	—6	15	2*	0
Brevital & #31777 ..... 4.0-10.0 cc.	60 (12 with EEg)	+14	—6	+6	12	6	48 (80%)

*Slow waves/spikes with Brevital occurred only in two trials. Others showed typical "sleep" patterns.
**This was dependent on extraneous noise or other stimuli.

ence with the original Compound #22451 indicated that the total length of sleep was much longer and that myoclonic features were much less evident than with the Compound #31777. It was then felt that a much longer treatment period could be developed if the compound were mixed with the anesthetic stereoisomer, Brevital. After a number of trials with Compound #31777, alone, the following preparation was administered: Brevital solution of 500 mg. per 30.0 cc. mixed with 1% solution of Compound #31777. To each injection dosage, gr. 1/150 atropine sulphate was added. Thus, equal parts of 16.5 mg. per cc. of Brevital and 10.0 mg. per cc. of Compound #31777 were administered.

Trials with 13 patients were undertaken at varying dosages and it was felt that from 6.0-10.0 cc. of the solution could be administered with ease to most patients. EEG observations using this combined solution were noted. It became apparent that the combined use of Brevital merely extended the anesthetic as well as the convulsant periods. Unpleasant reactions such as the actual experience of twitching ("shakes") and confused irritability were avoided and the reaction picture more closely resembled that found previously with Compound #22451. Therapeutic trials were carried on in 17 patients, one to four times a week for a three to four week period.

Findings

Previously reported preliminary work with Compound #22451, the original ultrashort acting oxy barbiturate preparation, was further elaborated in the present work. Electroencephalographic and clinical findings were described (Table I). It was further confirmed that Compound #22451 possessed powerful convulsant and anesthetic properties. The clinical findings indicated a production of almost instantaneous sleep with 2.0-4.0 cc. of a 1.65% solution. The EEG pattern provided evidence of distinct analeptic reactions with practically no external clinical manifestations of seizure. Awakening was rapid and without after affect.

Except for a 10-12 second period of apnea, as is common for most anesthetics, and was noted with all the preparations herein described, the pulse, respiration and blood pressure changes were insignificant throughout. Color was always good in all of the trials and no oxygenation was ever required. The EEG pattern resulting from Compound #22451 showed fairly typical dysrhythmic "activation" in the known epileptic patients and gave tentative localization data in known cases of central nervous system pathology. Although this feature needs more study it was apparent that "activation" studies in these particular EEG's should extend through the period of sleep, after the initial induction of slow wave/spike reactions. In several instances the localization information was ascertained from the pattern just prior to awakening. This was also found in using Compound #31777 alone, and with Brevital.

The clinical neurologic findings with Compound #31777 used alone and with Brevital, take into account the short time of reaction of Compound #317777. Sequentially, it was noted that in about ten to twelve seconds following 2.0-3.0 cc. injection the eyes would show nystagmus then fixation with mid-dilatation or full dilatation. With or without generalized myoclonic twitches there would be found paratonic resistance or rigidity to passive movements of neck, trunk, extremities and eyelids; at times this would result in hyperopposition movements in the extremities and eyelids. In almost all cases positive Hoffman's and Babinski's signs were elicited, at times even upon awakening. Sudden passive movements of trunk or extremities and other stimuli such as noise resulted in partial extensor twitches. Even without such stimuli a "secondary" burst of myoclonic twitches occurred in about three minutes, or just prior to awakening.

When Compound #31777 was identified as the more convulsant stereoisomer constituent of the original parent substance it was described as perhaps the most powerful intravenous barbiturate ever produced.[3] Recommended dosage limits were given as 2.0-

4.0 cc. of the 1% solution and this was not exceeded in using this compound alone.

Administration of 2.0-4.0 cc. of Compound #31777 (20.0-40.0 mg.) at the rate of 1.0 cc. per ten seconds resulted in facial or generalized myoclonic twitching of mild intensity and amplitude. No tonus could be discerned. The picture usually resembled a brief, curarized seizure, lasting from 20 to 40 secs., at times for longer intervals. Deep sleep ensued for about three minutes. In several instances the twitching started before sleep. Immediately preceding arousal, in most instances, another brief period of myoclonic twitching occurred. The latter, infrequently continued after waking. A brief startle, then clarity and a desire to get out of bed were noted. If the twitchings were experienced while a patient was still not anesthetized or after partial waking some complaints of uneasiness would be voiced. Otherwise descriptions of the subjective experience would be that of brief sleep or even a denial that sleep had occurred. Several instances of hiccup arose which lasted from twenty seconds to the time of arousal. No complaints of any vertigo, visual or gastro-intestinal disturbances were voiced.

The EEG pattern showed,, on induction, intense generalized slow wave activity with much less spiking or superimposed spikes than noted with Compound #22451. The duration of sleep and of analeptic reaction was half as long. The difference in pattern induced by the addition of Brevital seemed to consist of increased spiking either occurring alone, or, intermingled with, or, superimposed on the giant slow waves observed in the use of Compound #31777 alone. Exact detailed analysis of the wave forms has not yet been done, but there was definite similarity to the patterns found in Compound #22451. Twitching was still evident in the majority of trials with the mixture.

In attempting to set up a therapeutic program using Compound #31777 it was found that the rapidity of reaction together with instances of startle reaction and experiences of "shakiness" caused uneasiness and increased depressive symptoms. Since it was not yet deemed feasible to increase the dosage, which might have prolonged the total time of reaction, it was decided to approximate more closely the reactions previously described in the use of Compound #22451 by giving a mixture of Brevital and Compound #31777. Previous extensive clinical experience with Brevital had shown it to be

EEG Study with Compound #31777

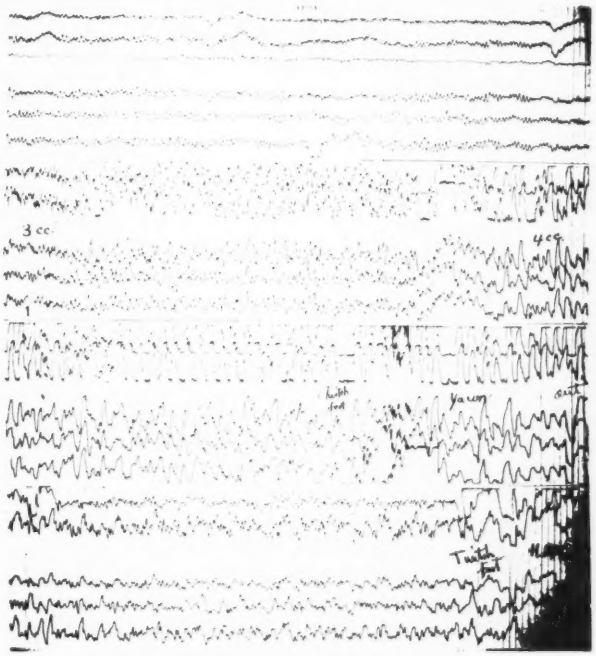

Figure 2. (H.McC.)—The Patient is a 32-year-old married woman, with repeated attacks of reactive depression over the past twelve years, associated with extreme fatigability alternating with agitation, and irritability. Present picture was one of depression with confused irritability, insomnia and almost complete anorexia for a week prior to study. Background of premature birth, sickly childhood and considerable retardation in school work. At time of examination, patient was very apprehensive, fearful, indecisive. Episodes of tearfulness and marked conflict were apparent. Previous attacks had been adequately treated within several weeks of intensive Amphetamine and Butisol medication. At the present illness there was no response to such medication and conditions seemed to be worse after three weeks of treatment. Increasingly violent altercations between patient, husband, and members of her family. EEG showed a normal resting pattern and at injection of 3.0-4.0 cc. an increasing spread of slow spike synchronous activity, which then changed after 4.0 cc. to a run of giant slow waves at 3/sec. or less, particularly in the frontal areas. Slow wave activity continued for approximately one minute at which time random slow waves or spikes, scattered, were noted and patient awoke. It was noted that at 3.0 cc. there was twitching particularly of the feet, with yawning. Prior to awakening, in less than four minutes, there was again a twitching of the feet, usually of a myoclonic type. Awakening with considerable clarity.

free of analeptic qualities. Comparative EEG's are noted in Table I and Figure 1. The subjective and clinical features immediately indicated more favorable responses. Anesthesia was noted before myoclonic twitches appeared and continued after the so-called secondary twitches preceding awakening. The EEG pattern of analeptic responses was twice as prolonged with evidences of stimulation at times persisting much longer, even into the waking state. The subjective reaction was described as relaxing sleep, alertness and a pleasant attitude on arising.

Figures 3 and 4 are examples of the effect of adding Brevital to Compound #31777.

With these considerations in mind it *was* felt entirely possible to set up a satisfactory and safe, efficient therapeutic routine in which the profound analeptic-anesthetic properties of Compound #31777 and Brevital could be employed on an ambulatory basis. (Table II—Therapeutic Results).

Discussion

In the previous and in the present preliminary reports on the actions of convulsant-anesthetic compounds it was brought out for the first time that optical stereoisomers of a barbiturate preparation have different pharmacologic properties. The parent Compound #22451, was found to produce simultaneous anesthesia and profound analeptic EEG responses. Pharmacologic differentiation of the parent substance made available for the present study a predominantly analeptic-anesthetic, Compound #31777. The experimental findings in previous animal work that Compound #31777 is probably the most powerful known anesthetic agent[3] also brought out the fact that convulsive manifestations accompany such potent anesthetic qualities. The relationship between anesthesia (sleep) and convulsive reactions is thus opened for more comprehensive study. In this work with Compound #31777 alone, the clinical and EEG analeptic reactions occurred almost simultaneously with the anesthetic and in some instances preceded and/or succeeded sleep. In the dosages employed, the total reactions

EEG Study with Brevital and Compound #31777

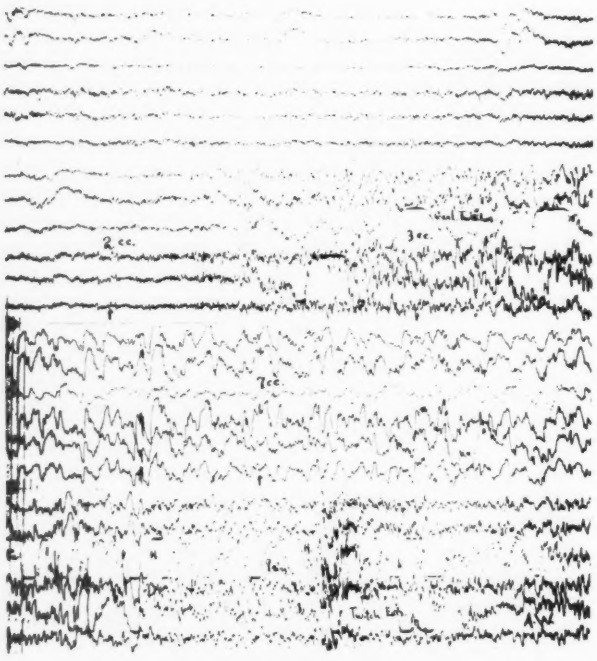

Figure 3. (A.W.)—24-year-old single girl, moderately dysplastic, history of severe diabetic illness in the family. Fairly acute schizophrenic illness developed approximately nine years ago, associated with marked confusion, disorientation, almost constant reactivity to vivid hallucinations and persecutory delusions. Originally treated by intensive ECT types of therapies and sedative measures. Gradual improvement with resumption of work habits after about two years of intermittent treatment. Patient was kept on maintenance ECT therapy for a considerable period of time. Several months prior to present study patient became involved with a love interest and was briefly engaged. Upon break-up of the engagement, patient displayed mounting anxiety and depression, with a brief period of acute hallucinatory reactions and screaming episodes.

Large dosages of chlorpromazine would usually be necessary to keep these outbursts under control. Some brief improvement under ECT and chlorpromazine, 100 mg. per day. However, she displayed more and more uneasiness, restlessness, tension, some episodes of weeping but without any of the aforementioned accessory symptoms. Resting EEG pattern revealed evidences of tension, synchronous fast waves (12-20/sec.) throughout. No pathologic slow wave activity, no localization, no sensitivity to hyperventilation or photostimulation. Injection of Brevital plus Compound #31777 at 2.0-3.0 cc. resulted in generalized twitching with a burst of synchronous slow spikes with superimposed fast spikes. This gradually changed to continuous giant slow wave activity, with some superimposition of fast spikes. Continuing to 8.0 cc. this pattern persisted for almost ten minutes at which time she again displayed episodes of generalized twitchings particularly in the extremities with some hiccup of mild type lasting for twenty seconds. She awakened in less than twelve minutes thereafter.

EEG Study with Brevital and Compound #31777

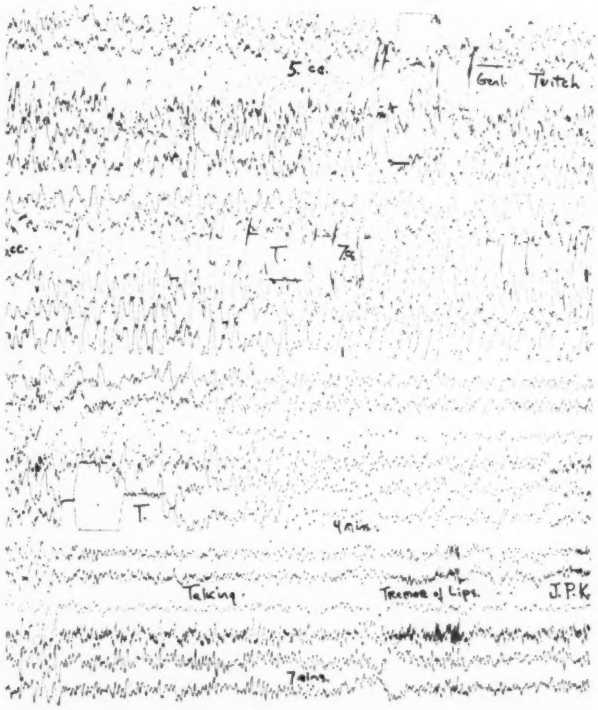

Figure 4. (J.P.K.)—24-year-old heavily built man, with intermittent anxiety symptoms and tensions throughout most of his recalled life. For the past five years before present study had shown episodes of severe panic every several months. Attacks of panic lasted about twenty minutes and associated with feelings of weakness in the limbs, needle-like sensations in the head and extremities, trembling and difficulty in breathing. At these episodes patient usually dashed home and reclined until discomfort subsided. He also suffered feelings of breathing difficulty at any occasion of unusual exertion. Physical findings had repeatedly been normal. At the time of present study, patient had been on Meprobamate 1600 mg. per day, for at least two years. Recent marriage seemed to bring out an increase in intensity and severity of the entire symptom picture. Also noted were fairly intense a agarophobic experiences, together with relative impotence. Clinical picture of visible anxiety, some difficulty in expressing himself, and instances of fearful depression. EEG study showed generally fast activity (14-24/sec.) with much spiking formation. Synchrony fairly well preserved, modulation practically absent. No sensitivity to hyperventilation or photostimulation, no localization noted. EEG pattern under combined solution, showed at 4.0-5.0 cc. sudden appearance of giant three per second slow waves with spikes and superimposed fast activity. Pattern became generalized at 5.0-6.0 cc. and for several minutes only giant slow waves (2-3/sec.) could be seen. Gradually over a period of four minutes the pattern broke up into occasional slow waves or spikes and then an occasional burst of slow waves lasting two seconds at a time. Patient awakened sufficiently to respond to questions in less than ten minutes. Secondary period of myoclonic twitchings usually of the face and lips could be noted just before awakening.

TABLE II

Therapeutic Results: Compound #31777

Patient	*Diagnosis*	*Wks. Tmt.*	*Results*
S.A.*	Colitis, severe phobic manifestations, agitated depression.	3	Mod. Imp. Temp.
R.K.*	Acute agitation, depression, severe abdominal conversion symptoms.	3	Mod. Imp.
H.McC.*	Recurrent reactive depression with moderate intellectual deficiency.	3	Increased Depression
R.J.C.	Chronic psychoneurosis with marked abdominal conversion symptoms.	3	Mod. Imp.
A.W.	Chronic schizophrenic, symptom free, secondary acute anxiety.	6	Much Imp.
J.P.K.	Chronic anxiety, with episodes of panic.	5	Recovered
R.M.	Chronic severe anxiety with abdominal conversion symptoms.	3	Much Imp.
G.K.	Agitated depression.	3	Recovered
L.B.	Moderately severe post concussion syndrome and sudden periods of somnolence.	2	Much Imp.
J.C.	Moderately severe post concussion symptoms.	3	Much Imp.
M.C.	Psychoneurosis, phobic anxiety type.	3	Mod. Imp.
A.C.	Obsession neurosis.	10	Much Imp.
A.H.	Chronic phobic anxiety	5	Not Imp.
S.K.	Chronic schizophrenic improved reactive anxiety.	4	Mod. Imp.
A.S.	Chronic schizophrenic, with acute hallucinations.	3	Not Imp.
K.R.	Chronic involutional agitation post hemiplegic.	6	Much Imp.
F.T.	Probable obsessive-compulsive neurosis.	4	Much Imp.
E.T.	Involutional reaction, moderately severe.	6	Increased Depression
R.A.	Acute and chronic depression.	2	Recovered
R.H.	Chronic reactive depression with many hysterical features.	3	Not Imp.
R.T.	Psychoneurosis, chronic recurrent anxiety with abdominal conversion, secondary addiction to Miltown & alcohol.	2	Much Imp.
A.F.	Acute phobic anxiety state.	4	Not Imp.

*These patients were started on Compound #31777 alone. The others were given the compound plus Brevital.

were found to be too rapid and the subjective responses too uncomfortable—for the emotionally disturbed patients but not for the patients investigated for organic disease of the central nervous system. The subjective reactions previously reported with the parent compound were pleasant and it was assumed that this must be due to the inclusion of anesthetic isomers in the parent substance viz. Brevital. In previously reported clinical and EEG-studies with Brevital, some of which were noted in the present work for comparison, the effect of Brevital was that of rapid, ultra-short acting anesthesia. No analeptic effect was produced externally or on the EEG. For further therapeutic purposes therefore, it was felt entirely feasible to mix Brevital and Compound #31777 in order to make the subjective reaction and cooperation easier. This was quickly ascertained in subsequent trials with the mixture. Myoclonic twitching was still evident in the majority of trials but without subjective awareness. The EEG patterns with this mixture indicated that analeptic effect, as well as anesthesia, was prolonged, and with the possibility that the former was intensified. At this point several questions might arise. From the standpoint of *activation* of the EEG, is the process herein described one of such rapid decortication that convulsive phenomena arise, or is rapid anesthesia (sleep) an irritative cortical state? Although much has been written regarding activation work this particular feature is still questioned. The recent experiments with Amytal and Metrazol by Ross and Morell[5] indicated a picture of light anesthesia superceded by convulsant reaction, two distinct processes. In fact, difficulty in the EEG study resulted when Metrazol overcame the sedative effect of Amytal. Some therapeutic experimental precedent might be noted in the work of LaVerne and Padula[6] and Karliner and LaVerne[7] who administered supra-maximal amounts of Pentothal and Metrazol or Megimide in rapid succession. Their therapeutic results were favorable enough to warrant further trial. EEG studies, using their technique were not reported here but again showed either anesthesia or convulsant reaction—or mutual dissipation of either effect if the drugs were given in rapid enough succession. In the findings presented with Compound #31777 and Brevital there seemed no doubt that profound anesthesia was simultaneous with convulsive reactions and that anesthesia did not decrease the latter.

The relative ease of admission, the subjective comfort and the safety of this induced convulsant-anesthetic action led to its use in psychiatric patients. There was, naturally, the background of long experience with convulsant therapies, of decidedly greater intensity than the procedure herein described.

Based upon previous experiences with various forms of convulsant therapy the procedure was adopted of administering the combination of Brevital and Compound #31777 as described and thus permitting a much longer period in which the patient experiences a definite alteration in consciousness but without any type of ataxic after effect or any amnesic reactions. This would make the procedure applicable in severe anxiety states. At the present time experience in the therapeutic usefulness is limited to relatively few patients. However, from the immediate effects upon the symptoms and certainly from the overall picture of alertness upon awakening from this type of sleep lends confidence to the procedure. In this work it was found that half of the patients showed at least relief of symptoms and a greater degree of hopefulness for their future than they had previously experienced. It was felt that the usefulness of this type of agent was quite distinct in the field of medical psychiatry. Two patients suffering from typical post concussion syndrome obtained remarkably rapid relief of symptoms. As noted in the previous work, the convulsant anesthetic reactions herein produced were of an entirely different quality than described with ECT, Metrazol and other barbiturate-stimulant procedures.

Clinically it was felt that Compound #31777 in conjunction with Brevital provided an alteration of consciousness, central

stimulation of convulsive type, with only gentle myoclonic responses and very rapid awakening as from a pleasant sleep. Ambulatory treatment is feasible with this procedure as are EEG activation procedures which may be rapidly performed. Brevital alone produced rapid sleep with rapid awakening but without any EEG reference to any type of convulsant activity. Compound #31777 brought out clinically very rapid sleep with more rapid awakening but with an EEG pattern of definite profound convulsant reactivity. It was felt that the combined solution could be eventually used repeatedly in a given day on a given patient to prolong the described effect with relative safety. Certain features still need clarification and are mentioned: The relationship between therapeutic efficacy and the duration of induced analeptic phenomena; the relative necessity of myoclonic responses (which probably could be controlled); the analysis of the induced EEG patterns and their relationship to therapeutic and activation results.

Acknowledgment: Eli Lilly and Company furnished Compounds #22451 and #31777 used in this work as well as the Brevital (methohexital, Lilly). The author gratefully acknowledges the helpful suggestions and criticisms offered by Doctors Ivan Bennett and C. M. Gruber, Jr., of Eli Lilly.

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DISCUSSION

Stimulatory Barbiturates in Psychiatry: Compound 31777

IVAN F. BENNETT, M.D.*

In discussing Dr. Friedman's paper it might be appropriate to relate what has been done in our laboratories with Compound 31777 and to review the clinical history of the stimulatory barbiturates.

I know of only one other stimulant barbiturate used in psychiatry. This is DMBEB or 5-(1, 3-dimethylbutyl)-5-ethylbarbituric acid. The first clinical report of DMBEB was by Gottlieb.[1] Noting temporary amelioration of depressive symptoms and the production of euphoria in schizophrenic patients following the intravenous administration of amobarbital sodium, originally described by Lindemann,[2] Gottlieb treated ten depressed patients with a single oral dose (50 to 150 mg.) of the sodium salt of DMBEB. In six an antidepressive or euphorogenic effect was observed in 1 to 1½ hours. A very good response was obtained in four. Unlike amobarbital sodium, DMBEB was seen to have long duration, lasting throughout the day or into the following morning. Side-effects, noted in six, included intense itching in three, nausea and vomiting, paresthesias and one abortive seizure, i.e., a transitory confusional state. In 1954, Pennes, on the basis of the therapeutic activity of intravenous amobarbital sodium in schizophrenic patients, administered DMBEB to 20 hospitalized cases, using an average intravenous dose of 63.5 mg.[3] There was a decrease in symptoms in 11 patients including four of the six pseudoneurotic ones who showed improvement in anxiety, depression, tension, irritability and hostility. The three obsessive-compulsive and seven of the fourteen overt schizophrenic patients showed a slight to moderate improvement. In six patients the same dose of DMBEB produced a greater therapeutic response than with an equivalent dose of amobarbital sodium. Pennes also reported a high incidence of side-effects; 18 of the 20 had severe and generalized itching for several minutes and two developed transitory myoclonic seizures without loss of consciousness. Both investigators concluded that the high incidence of adverse reactions prohibited further clinical trial of DMBEB.

For many years barbiturate chemists have been looking for a more satisfactory ultrashort-acting anesthetic barbiturate. In 1955, after more than 2000 compounds had been synthesized and tested in animals, Compound 22451 was selected for clinical trial.[4] This is a stereoisomeric mixtures of the sodium salt of 1-methyl-5-(1-methyl-2-pentynyl)-5-allyl-barbituric acid. The molecule contains two asymmetric carbon atoms, thus, two *dl* pairs (*alpha* and *beta*) exist and each pair is resolvable into optically active *d* and *l* forms. The four stereoisomers

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Compound #22451

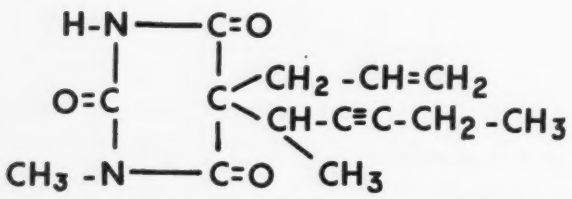

Figure 1. 1-Methyl-5-Allyl-5 (1-Methyl-2-Pentynyl) Barbituric Acid.

have now been prepared. Compound 22451 differs from other anesthetic barbiturates in that it contains no sulphur in the molecule, has two positions of unsaturation in the 5-position radicals, and contains a methyl group on one of the ring nitrogen atoms (Figure 1). It is the first barbiturate to show significant differences in potency between optical antipodes. Its use as a short-acting anesthetic for EST was described by Gruber et al.[5] Friedman, in EEG studies on 20 patients, noted a central stimulation of a convulsive type without the so-called strain of a convulsive seizure.[6] He recognized the stimulatory reactivity of the compound and, with the successful resolution of the stereoisomers, was enabled to evaluate therapeutically the sodium salt of the *beta-1* isomer (Compound 31777). This is the most potent anesthetic barbiturate examined in our laboratory.

Incidentally, the sodium salt of the *alpha-dl* isomer, methohexital, is being well received as an ultra-ultrashort acting barbiturate anesthetic. Compared with other intravenous anesthetic agents, methohexital exhibits greater potency (two to five times), shorter duration of effect (half as long) and more prompt subject recovery, even after large doses. Friedman has previously reported on its use as a pre-shock anesthetic and on its superiority to the thiobarbiturates in this procedure in terms of the absence of the unpleasant smell-taste experience, rapidity of anesthesia and of awakening.[7,8]

In Gibson's animal experiments anesthesia with Compound 31777 was promptly induced and was satisfactory, but hyperirritability during the recovery phase was noted in the rat and the dog but not in the monkey. Auditory and tactile stimuli initiated a brief episode of myoclonic twitching before the animal had regained its upright position. While all showed approximately the same degree of anesthesia, the degree of post-anesthetic excitement decreased with time. It was believed that this did not reflect increased tolerance but was merely due to the dog's learning that by lying quietly until his motor equilibrium had been restored he could avoid bumping into objects.[4] This urge to "get up and go" was also observed by Friedman in his patients.

Inspired by Dr. Friedman's idea and seeing a possible similarity in action between Compound 31777 and the stimulant barbiturate DMBEB which had been shown to be effective, to some extent, in the depressed and acute schizophrenic patient with anxiety-depression, I evaluated a small sample of such individuals at the Marion County General Hospital, Indianapolis; 50 mg. of Compound 31777 in 5 cc. of sterile distilled water was rapidly given intravenously five days weekly for a series of ten treatments. Patients were observed for 30 minutes after administration for side-effects and clinical observations were made during the rest of the day for behavioral changes. The drug was easily administered without pre-treatment apprehension or post-treatment confusion or headaches. Good respiratory exchange and color were maintained during the procedure. The patients spontaneously commented on the pleasant and rapid falling off to sleep and upon the relaxation and general feeling of rest and comfort on awakening. One agitated depressed patient

TABLE I

I—Depressed Patients

31777 STUDY

Sex & Age	D.X.	Pre-Treat. & Dur.	Post-Treat. & Dur.	Clinical Result
M–58	R. D.	Thor.–1 wk.	EST–9	D
F–63	R. D.	None	EST–8	"
M–56	R. D.	"	Imipramine 3 wk. → EST–8	"
M–68	R. D.	"	EST–12	"
F–63	I. M.	"	Imipramine 4 wk. → EST	I

R.D. = Reactive Depression
I.M. = Involutional Melancholia
D = Discharged
I = Improved

TABLE II

II—Miscellaneous Patients

31777 STUDY

Sex & Age	D.X.	Pre-Treat. & Dur.	Post-Treat. & Dur.	Clinical Result
M–37	Ac.P.S.	Trifl.–6.5 wk.	EST–12	Trans. V.A.H.
F–23	Ac.P.S.	Thor.–5 wk.	None	Disch.
EEG's				
M–34	Ch.P.S.	Thor.–2 wk.	"	"
M–51	In.Per.	Thor.–4 wk.	"	"

Ac. P.S. = Acute Paranoid Schizophrenia
Ch. P.S. = Chronic Paranoid Schizophrenia
In. Per. = Inadequate Personality
Trifl. = Trifluoperazine
Thor. = Thorazine

continued requesting the "magic shots" although she had shown no objective improvement following the course of treatment. Those who improved noted a gradual prolongation of the post-treatment interval of the reduced anxiety, irritability and hostility. The rapid onset of anesthesia shows that the drug is immediately effective upon reaching the brain. Average onset for anesthesia was 32 seconds and the average duration was five minutes.

Clinical results in this small group cannot be considered significant but they do suggest indications for its use and speak well for the gathering of data on a larger series (Tables I, II). It can be seen from the table of results that depressions were not helped and required EST for successful remission.

Compared with methohexital which, in one study, caused slight twitching in three out of 24 administrations,[9] Compound 31777 produced this in all of the patients and 50% of the treatments were associated with this phenomenon as the patient went into or came out of the anesthesia (Table III). A few had transient laryngospasm or a cough reflex, some secondary to excessive salivation. Two patients experienced dysarthria for five to ten minutes following the treatment. The stuttering was alarming for it had never been experienced previously. Its short duration and simple reassurance, however, eliminated the secondary anxiety. Side-effects were transitory and minor. They required no ancillary measures for prevention or control.

EEG studies were done on seven patients who received 50 mg. intravenously of Compound 31777 on one day and 50 mg. intravenously of methohexital on the day following. The fourteen tracings were coded and interpreted blindly by Dr. Philip White (Department of Neurology, Indiana University School of Medicine). Table IV shows that his interpretations were remarkably accurate in the differentiation of the EEG activity of the two drugs. EEG tracings from a patient 80 seconds after the administration of each drug pointed up the differences between them (Figures 2,3).

Doses approximately equipotent, i.e. in relationship to depth of anesthesia, of Compound 31777, methohexital, and thiopental sodium were administered to a cat and subcortical tracings were re-

TABLE III

Side-Effects

31777 STUDY

Patient	Twitching	Laryngo Spasm	Hiccough	Stuttering
M–58	3/8	4/8		
F–63	3/11	1/11		
M–56	4/11	3/11	1/11	
F–63	6/11			
M–37	8/11			
F–23	3/11			3/11
M–34	10/11			2/11
M–51	5/8	5/8	3/8	
Totals	42/82	13/82	4/82	5/82
%	51.2	15.9	4.9	6.1

TABLE IV

Human Electroencephalographic Results

31777 STUDY

Patient	No Change	Inc Hi Ampl Fast Activity C Some Intermixed Slowing	Inc Hi Ampl Slow Act C Superimpose Fast Activity of Variable Voltage
M–58		25398	31777
F–63		25398	31777
M–56		25398	31777
M–37	25398		31777
F–23		25398	31777
M–34		25398	31777
M–51		25398	31777

25398—Methohexital, Lilly

31777 Study

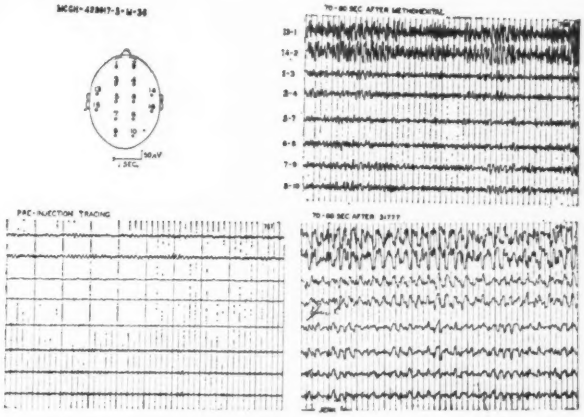

Figure 2. Representative EEG tracings following I.V. injection of 50 mg. of either 31777 or Methohexital.

31777 Study

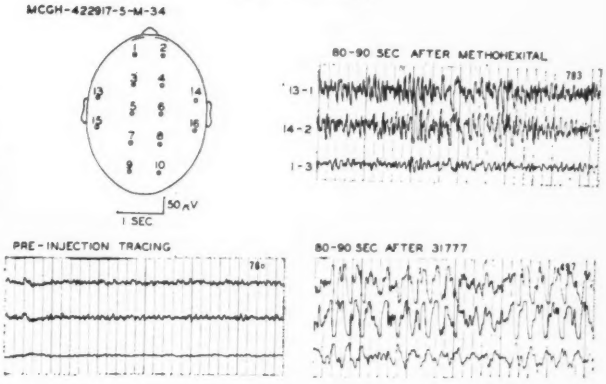

Figure 3. Representative EEG tracings following 50 mg. I.V. injection of either 31777 or Methohexital.

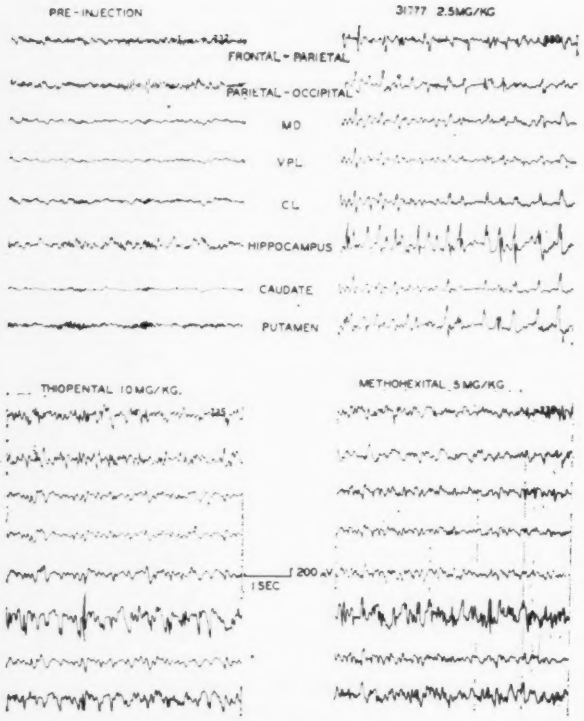

Figure 4. Comparative EEG tracings from male cat No. 25 (3.8 kg.) one minute after I.V. injection.

corded (Figure 4). During the arousal period the cat's EEG with Compound 31777 showed 4-cycle per second waves with some superimposed fast activity. Methohexital produced an 8-cycle per second and thiopental sodium a 16-cycle per second activity (Figure 5). On recovery, the cat continued to show the high voltage and slow activity of 8-cycle per second waves, while the methohexital tracing had increased to a 24-cycle per second and the thiopental sodium one to a 32-cycle per second pattern (Figure 6). The absence of the typical barbiturate fast activity would suggest a minimal cortical response and a primary localization in the deeper centers. Hippocampal activity with all three was noted one minute after injection, but was present during the recovery phase only with Compound 31777. In addition, this compound continued to act upon the thalamic nuclei during the arousal phase. However, this activity was disappearing as the animal recovered. The high degree of similarity between methohexital and thiopental sodium and the marked difference between them and Compound 31777 are clearly evident.

In my opinion Compound 31777 is an exceedingly interesting drug. I feel we should be grateful to Dr. Friedman for reviving interest in the stimulatory barbiturates. This group of compounds may turn out to be not only of academic importance but also of therapeutic usefulness.

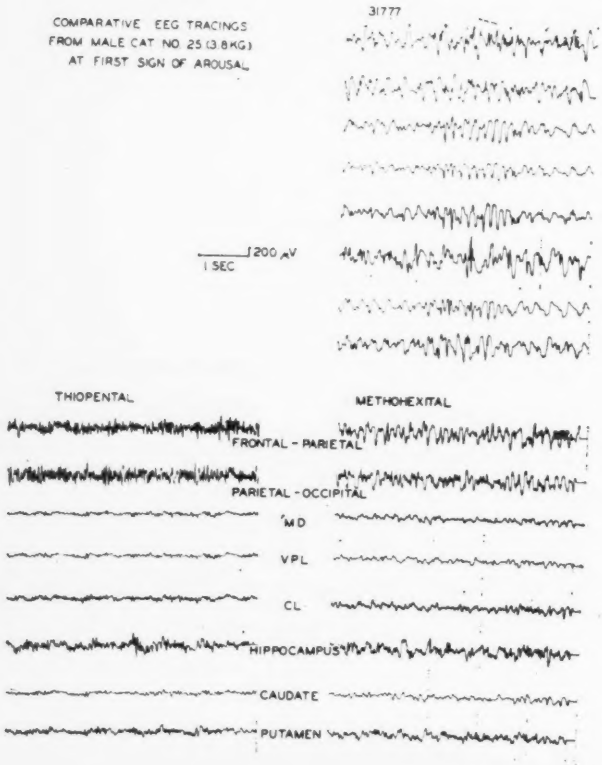

Figure 5. Comparative EEG tracings from male cat No. 25 (3.8 kg.) at first sign of arousal.

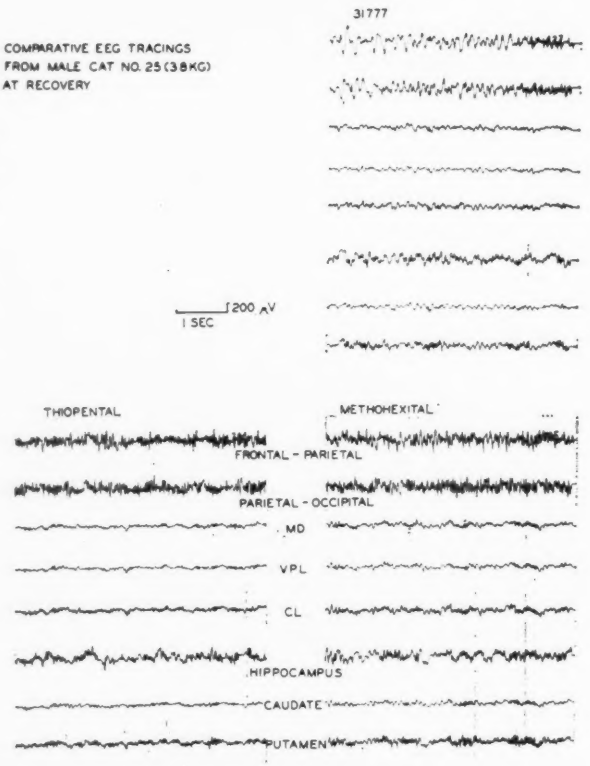

Figure 6. Comparative EEG tracings from male cat No. 25 (3.8 kg.) at recovery.

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Fluphenazine: Comparative Studies

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For the last several years a continuous drug evaluation program has been underway at the Danvers State Hospital. Its superintendent, Dr. Peter B. Hagopian, evaluated chlorpromazine,[7] and Dr. Francis X. Sullivan, the assistant superintendent, has worked with thiopropazate. The writers have been evaluating other drugs and, as a result of the work on several compounds at the same hospital, it has become possible to make an attempt at comparative evaluation of fluphenazine as compared with several other phenothiazines.

Comparison With Trifluopromazine

A random study of 110 fluphenazine cases having previously been made, a similar study in 100 patients taking triflupromazine was undertaken, with as close an approximation in diagnosis, age, and duration of illness as possible. Table I, II, III, V, and VI compare respectively duration diagnosis, age, improvement, and side effects on a percentage basis between the two drugs.[4] Table IV gives a breakdown of the triflupromazine dosage, the average maintenance dose being 208.8 mg. daily. The average dose of fluphenazine was 12.8 mg. daily, one-sixteenth the dose of triflupromazine and half what one would expect as the result of pharmacological studies,[1] particularly as the results were better with the fluphenazine.

There were more extrapyramidal side effects due to the fluphenazine. The percentage of those observed in the case of triflupromazine corresponded with those reported by Hagopian[7] due to chlorpromazine. There was more depression, lethargy, and akathisia due to fluphenazine. Approximately 15% of the patients in each series were taken off the respective medications due to side effects. In the case of triflupromazine 5% were taken off due to extrapyramidal symptoms and the same due to depression; 11% of patients were taken off fluphenazine due to extrapyramidal side effects. The hypertension case is discussed elsewhere.[5]

A comparative study of side effects comparing prochlorperazine and triflupromazine[5] had shown such promising results that it was felt that the latter drug might have enough vagolytic effect to offset the pronounced tendency of the piperazine-promazines to produce extrapyramidal side effects. Accordingly the ten patients in the preliminary fluphenazine study who had such severe parkinsonism that they could not be maintained on the drug had their doses of it

halved and ten times the amount of triflupromazine was added. Complete relief was obtained in four cases and partial alleviation in the fifth. The same was done in two cases having jaw spasms and in one case only was the combination effective. There were negative results in three akathisia cases and in one with polyuria. Average starting dose in these patients was 18.3 mg. daily before the dose of fluphenazine was halved and the triflupromazine added. Since the combination was ineffective in seven of the seventeen cases in which it was tried, its use was abandoned as not being clinically effective enough even to test further.

Aliphatic and piperazine promazines were combined by Kruse[9] in a study of 38 cases, using chlorpromazine and trifluoperazine, in average doses of 150 mg. and 20 mg. a day respectively. Most of the patients were chronic regressed schizophrenics. Results were not remarkable except that in combining the drugs a greater therapeutic effectiveness may be achieved than with a comparative dose of each single drug. Percentage of disturbing extrapyramidal side effects were greater than found with chlorpromazine and less than with trifluoperazine alone.[8]

TABLE I

Duration of Illness in Years	% Triflupromazine Patients	% Fluphenazine Patients
0 - 1	17	20.9
1 - 2	23	11.8
2 - 5	13	22.7
5+	47	44.5

TABLE II

Diagnosis	% Trifluopromazine Patients	% Fluphenazine Patients
Schizophrenia	61	53.6
Mental Deficiency with Psychosis	5	13.6
Chronic Brain Syndrome	8	13.6
Manic-Depressive	3	6.3
Personality Disorder	1	5.4
Psychoneurosis	1	4.5
Involutional Reaction	2	1.8
Paranoid Condition	2	0.9
Acute Brain Syndrome	2	—

TABLE III

Age	% On Triflupromazine	% On Fluphenazine
16 - 20	4	3.6
21 - 25	4	1.8
26 - 30	3	10.0
31 - 35	10	4.5
36 - 40	14	8.2
41 - 45	5	12.7
46 - 50	15	7.3
51 - 55	10	10.0
56 - 60	5	10.0
61 - 65	11	10.9
66+	12	20.8

TABLE IV

Dosage of Trifluopromazine

Mg./Day	Maximum	Maintenance
25	2	7
50	1	12
75	6	6
100	10	27
150	18	13
200	21	16
300	20	10
400	11	3
600	3	–
800	4	4
900	1	–
1000	2	1
1200	1	1

TABLE V

Improvement

	Triflupromazine	Fluphenazine
Home or Parole	16	10.9
Maximal	10	15.5
Moderate	21	34.5
Minimal	17	15.5
None	36	23.6

TABLE VI

Side Effects

	% With Triflupromazine	% With Fluphenazine
Parkinsonism	23	31.8
Lethargy	4	9.1
Depression	5	7.3
Akathisia	4	7.3
Equilibrium Disturbance	1	3.6
Neurocirculatory Collapse	1	3.6
Leukopenia	1	3.6
Propulsion	–	1.8
Edema	–	1.8
Blurring of Vision	–	0.9
Polyuria	–	0.9
Rash	3	0.9
Nasal Congestion	–	0.9
Flushing	–	0.9
Tachycardia	2	–
Fulminating Hypertension	1	–
Dysphagia	1	–
Conculsions	1	–

Comparison with Prochlorperazine and Thiopropazate by Substitution of Medication in Chronic Disturbed Patients

In 62 patients (29 had been on treatment with prochlorperazine and 33 with thiopropazate) medication was discontinued and they were placed on fluphenazine, in about one-eighth the dose. They were on the three chronic disturbed wards of the female psychiatric service of the Danvers State Hospital, and comprised all patients who had been treated with prochlorperazine and thiopropazate six months or more. Five of the patients had been in the hospital 3-5 years; ten 5-10 years; 18 had been hospitalized 10-20 years; and the remainder had been hospitalized more than 20 years; 46 patients were schizophrenics; eight were mental deficients with psychosis; five had chronic brain syndrome; one had psychopathic personality with psychosis. All the patients were more than 33 years of age; four of them were over 65 years of age.

Patients are distributed on these wards according to behavior. In the least disturbed ward, of 23 patients whose medication was changed, ten were moderately improved, three minimally improved and three worse. When medication of 19 patients in the moderately disturbed ward was changed, six were moderately and one minimally improved. Twenty were changed in the most disturbed ward; six were moderately and one minimally improved. Of the total 62 patients there were 21 moderately improved, six minimally improved, and three worse; the remaining 32 were unchanged.

Of the 29 patients changed to fluphenazine from prochlorperazine 14 were moderately improved, two minimally improved, and two worse. Of the 33 patients changed from thiopropazate, seven were moderately improved, four minimally, and one worse. The proportion on each ward on prochlorperazine and thiopropazate was approximately equal.

Criteria of improvement were fairly strict. Minimal improvement was judged as cessation of at least one outstanding symptom of disturbed or destructive behavior, such as breaking windows, denudativeness, or assaultive episodes. Moderate improvement was judged by cessation of several such symptoms plus improvement in mental content and initiative.

Dosage of prochlorperazine varied between 10 mg. and 200 mg. daily, and that of thiopropazate between 10 mg. and 80 mg. Average dose of the former was 71 mg. and the latter 30 mg. Fluphenazine dosage varied between 2.5 and 40 mg. daily. In the patients changed to fluphenazine from prochlorperazine the average dose of the former was 8.6 mg. daily after three months on the new drug, and 8.0 daily in the case of thiopropazate. Average dose for the entire 62 patients was 8.28 mg. daily. The fluphenazine-prochlorperazine dosage ratio was 1: 8.25, and the fluphenazine-thiopropazate ration was 1 : 3.75. There was no significant overall difference in ratio between the improved and unimproved patients. Some remained unimproved on more than the proportionate dose of fluphenazine and some improved on less. Despite the difference in dosage ratio, therapeutic effectiveness in the two groups was about equal at the same average dose. Average dose in the preliminary fluphenazine study[4] was 12.8 mg. daily for maintenance; 37.2% of those patients were given 15 mg. daily or more, while in the present study 19.3% took 15 mg. or more. This would account for the difference in average dose in the two series of cases.

Four patients having no extrapyramidal side effects when taking prochlorperazine developed them when taking fluphenazine, and the reverse was true in a like amount of patients. One patient taking thiopropazate developed extrapyramidal effects when put on fluphenazine, and two ceased to have them.

Comparison With Perphenazine

In a series of 100 patients taking perphenazine at Danvers State Hospital,[2] 75 were chronically disturbed. All the patients described in the study above were chronically disturbed as were 44 patients in the preliminary fluphenazine study.[4] Chronic disturbed patients, therefore, comprised 62% of the total 172 patients given fluphenazine.

In the perphenazine group 71% of the patients were schizophrenics; in the fluphenazine groups there were 64%. In the perphenazine group 16% were mental deficients with psychosis; there were 14% with this diagnosis in the fluphenazine groups. In the perphenazine group 8% had chronic brain syndrome; 12% of the fluphenazine group were so afflicted. Those having other disorders were statistically insignificant. Age and duration of illness were similar.

Of the 75 chronic disturbed patients taking perphenazine about a third were discontinued due to extrapyramidal symptoms and another third due to no significant clinical improvement. Average maintenance dose was 29 mg. daily. Over-all improvement was 26%; 91% of the patients had been treated with other drugs, mostly chlorpromazine and reserpine. Over-all improvement when changed from thiopropazate and prochlorperazine to fluphenazine was 43.6%.

Average daily dose given the 172 patients taking fluphenazine was 11.8 mg. daily. The dosage ratio as compared with perphenazine was 1 : 2.6. Over-all fluphenazine improvement was 65% in all patients, and 44% in the case of perphenazine.

Because they had been on piperazine-promazine compounds before taking fluphenazine, the 62 chronically disturbed patients discussed in the previous section cannot be considered in comparing side effects statistically. Of the 110 cases discussed in the preliminary fluphenazine study 43.2% had extrapyramidal side effects as compared with 41% of the 100 perphenazine patients. The side effects were more easily controllable in the fluphenazine cases, and this probably accounts for the larger percentage of improvement as more patients could be given an optimum dose and fewer discontinued.

Comparison With Trifluoperazine

Differences in dosage between trifluoperazine and fluphenazine have been previously noted.[4] Mean doses have since been reported in all-schizophrenic studies. Macdonald reports 20-25 mg. daily, and Kruse[5] 40 mg. daily. In the latter study approximately 70% of the cases were chronic, and over-all improvement was 89.8%. Over-all improvement in the preliminary fluphenazine study[4] was 71.4%; only 59% of these cases were schizophrenics, and the percentage of improvement was probably less because there were 15% each of chronic brain syndrome and mental deficiency with psychosis in the latter study.

Summary

1. Fluphenazine was compared with triflupromazine and found to be more effective therapeutically at one-sixteenth the dose, but with more extrapyramidal side effects.

2. Fluphenazine was compared with and found more effective than prochlorperazine, thiopropazate, and perphenazine, at approximately one-eighth, one quarter and two-fifths of the respective doses. There was not much difference in the incidence of extrapyramidal side effects; they were more controllable in the case of fluphenazine than in perphenazine.

3. Fluphenazine-triflupromazine and trifluoperazine - chlorpromazine combinations were tried in an attempt to reduce side effects of the piperazine-promazine compounds. Side effects were found to be less in these combinations than in the case of fluphenazine and trifluoperazine given alone and more than in the case of triflupromazine and chlorpromazine given alone.

4. Extrapyramidal side effects seem fixed with equal doses of the same drug, with slight exception. After treatment with antiparkinsonian agents or reduction of dosage, side effects tend to recur after discontinuance of the antiparkinsonian agents or resumption of the previous dosage.

5. Trifluoperazine is as effective, at least, as fluphenazine, but in at least double the dosage.

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The triflupromazine used in these studies was supplied by the E. R. Squibb and Sons under the trade name Vesprin. The fluphenazine was supplied by the same company under the trade name of Prolixin.

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